

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203137Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203137

SUPPL #

HFD # 160

Trade Name Vizamyl

Generic Name flutemetamol f18 injection

Applicant Name GE Healthcare

Approval Date, If Known

### **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:

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

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES

!

!

! NO

! Explain:

Investigation #2

IND #

YES

!

!

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

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: 10/3/13

Name of Office/Division Director signing form: Libero Marzella, MD, PhD  
Title: Division Director (Acting), Division of Medical Imaging Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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  
10/03/2013

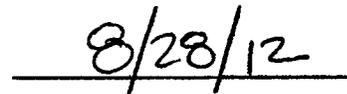
LIBERO L MARZELLA  
10/04/2013

**1.3.3 Debarment Certification**

GE Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application for NDA 203137, Flutemetamol F 18 Injection.

A handwritten signature in black ink, appearing to read "Yamo Deniz", written over a horizontal line.

Yamo Deniz, MD, Clinical Development Leader

A handwritten date "8/28/12" written in black ink over a horizontal line.

Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203137 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: VIZAMYL Established/Proper Name: flutemetamol F 18 Dosage Form: Injection: 150 MBq/mL		Applicant: GE Healthcare Inc. Agent for Applicant (if applicable):
RPM: Sharon Thomas		Division: DMIP
<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>	
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>October 26, 2013</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 checked="" type="checkbox"/> None	

<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 checked="" type="checkbox"/> Standard <input 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>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>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 <input type="checkbox"/></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 checked="" 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) Approval 10/25/2013
<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>	10/15/2013
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	10/26/2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	NA

<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>	10/3/2013 (Vial/Shield Labels)
<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>	Proprietary Name-Conditionally Acceptable -02/14/2013 Proprietary Name Review-02/14/2013
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 12/06/2012 <input checked="" type="checkbox"/> DMEPA 03/26/2013 <input checked="" type="checkbox"/> DMPP/PLT 06/22/2013 <input checked="" type="checkbox"/> ODPD 05/31/2013 <input checked="" type="checkbox"/> SEALD 09/15/2013 <input type="checkbox"/> CSS N/A <input type="checkbox"/> Other reviews Maternal Health Team: 10/11/2013
<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>	12/04/2012
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2) <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
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)           <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>05/08/2013</u> If PeRC review not necessary, explain: <u>N/A</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

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

<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>	10/3/2013 09/12/2013 09/09/2013 09/04/2013 08/30/2013 08/05/2013 07/17/13 07/01/2013 06/28/2013 06/17/2013(DARRTS) 05/09/2013 (DARRTS) 04/02/2013 (DARRTS) 03/22/2013 03/24/2013 03/22/2013 (2) 03/11/2013 (DARRTS) 03/07/2013 03/01/2013 (DARRTS) 02/27/2013 (DARRTS) 01/02/2013 12/14/2012 12/12/2012 (DARRTS) 12/04/2012 (DARRTS) 12/01/2012 (DARRTS) 11/16/2012
<ul style="list-style-type: none"> <li>❖ Internal memoranda, telecons, etc.</li> </ul>	
<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 checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i></li> </ul>	<input type="checkbox"/> No mtg 04/12/2012
<ul style="list-style-type: none"> <li>• EOP2 meeting <i>(indicate date of mtg)</i></li> </ul>	<input type="checkbox"/> No mtg 09/7/2010
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i></li> </ul>	Guidance- 10/25/2013 Late Cycle- 07/23/2013 Mid-Cycle- 04/02/2013
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available <i>(do not include transcript)</i></li> </ul>	
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None 10/21/2013
<ul style="list-style-type: none"> <li>Division Director Summary Review <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None 09/16/2013
<ul style="list-style-type: none"> <li>Cross-Discipline Team Leader Review <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None 09/16/2013
<ul style="list-style-type: none"> <li>PMR/PMC Development Templates <i>(indicate total number)</i></li> </ul>	<input checked="" type="checkbox"/> None

<b>Clinical Information<sup>6</sup></b>	
<b>❖ Clinical Reviews</b>	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	06/28/2013(concurrence, see clinical review)
• Clinical review(s) ( <i>indicate date for each review</i> )	06/28/2013 Filing 12/03/2012 ( with TLs concurrence)
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR</b> 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> )	06/28/2013(see clinical review)
<b>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)</b>	<input checked="" type="checkbox"/> None
<b>❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)</b>	<input checked="" type="checkbox"/> Not applicable
<b>❖ Risk Management</b> • REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> ) • REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> ) • 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> )	<input checked="" type="checkbox"/> None
<b>❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)</b>	<input type="checkbox"/> None requested 05/03/2013 04/26/2013 04/29/2013
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
<b>❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)</b>	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
<b>❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)</b>	<input type="checkbox"/> None 06/29/2013 (concurrence, see statistical review)
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/29/2013 (concurrence, see statistical review)
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/29/2013, Filing 11/30/2012( with TLs concurrence)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<b>❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)</b>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/26/2013 (concurrence, see clinical pharmacology review)
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/26/2013, Filing 12/10/2012( with TLs concurrence)
<b>❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)</b>	<input checked="" type="checkbox"/> None

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

<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
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/27/2013 (concurrence, see pharm/tox review)
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/27/2013, Filing 12/01/2012( with TLs concurrence)
❖ 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
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI 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 10/23/2013
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 06/28/2013 (concurrence, see product quality review)
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Addendum- 10/16/2013 06/28/2013, Filing 11/16/2012( with TLs concurrence)
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 06/20/2013, Filing 11/09/2012 (with TLs concurrence)
<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> )	N/A
❖ 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</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See CMC/ product quality review, page 116.
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report) (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: 10/02/2013 <input checked="" 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 type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" 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  
10/29/2013

**Team /Labeling Meeting  
May 7, 2013**

**NDA 203137 (PDUFA V- “Program”)**

**Product:** Vizamyl (Flutemetamol F18 Injection)  
**Sponsor:** GE Healthcare  
**Proposed New Indication:** PET imaging for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment.  
**Subject:** Internal Labeling Meeting

**1. Team:**

- Rafel Rieves, MD, Director, Division of Medical Imaging Products (DMIP)
- Ibero Marzella, MD, Deputy, Division Director, DMIP
- Alex Gorovets, MD, Clinical Team Leader, DMIP
- Lucie Yang, MD, PhD, Primary Medical Team Leader, DMIP
- Phillip Davis, MD, Primary Reviewer, DMIP
- Eldon Leutzinger, PhD, CMC Team Leader, ONDQA
- Ravindra Kasliwal, PhD, CMC Reviewer, ONDQA
- Robert Mello, PhD, Microbiologist, OPS/NDMS
- Jyoti Zalkikar, PhD, Statistical Team Leader, DMIP
- Lan Huang, PhD, Statistical Reviewer, DMIP
- Sally Hargus, PhD, Pharm/Tox Reviewer, DMIP
- Gene Williams, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCP5
- Christy John, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCP5
- Ira Krefting, MD, Safety Deputy Director, DMIP
- CDR Sandra Rimmel, OSE Regulatory Project Manager
- Kevin Wright, Pharm D, DMEPA reviewer
- Joyce Weaver, PharmD, DRISK reviewer
- Sharon Thomas, (RPM)

**2. Sections covered include:**

- **Section 7- Clinical Pharmacology-** To research to provide drug interaction info.
- **Section 12.1- Pharm/Tox** -To review/confirm if Flutemetamol does not bind to tau protein in in vitro studies.
- **Section 14.1- Clinical-**To confirm if co-registration was not utilized....separate CT or MRI scans were obtained
- **Section 14.1-Stats-**To check/confirm numbers with GE (first and second paragraphs under Table 5, to revise columns in Table 6 to add Autopsy data, to confirm results in studies one and two for Tables 7 and 8, to revise descriptors in Table 8.

**3. Milestones:**

MILESTONES	MILESTONE DEADLINES	MEETINGS
Receipt Date	October 26, 2012	
Day 45	December 10, 2012	<a href="#">Filing/Planning Meeting</a> Dec. 3
Day 60 (Filing Date)	December 24, 2012	
Day 74 Letter Due	January 8, 2013	
Team Meeting		Jan. 24, 2013 [Thurs.]

**Team /Labeling Meeting  
May 7, 2013**

Team /Mid-Cycle Practice #1		Feb 19, 2013 [Tues.]
Team /Mid-Cycle Practice #2		March 7, 2013 [Thurs.]
Month 5- Mid-cycle	March 25, 2013	<a href="#">Mid-cycle Meeting</a> March 19
Mid-cycle –Communication Mtg	April 9, 2013	<a href="#">Mid-cycle Communication Mtg</a> April 2
Labeling Meetings		Apr. 9, 2013 [Tues.]
		April 23, 2013 [Tues.]
		May 7, 2013 [Tues.]
		May 21, 2013 [Tues.]
		June 6, 2013 [Thurs.]
Send Labeling to GE	July 8, 2013	
Late Cycle Pre-Meeting	July 14, 2013	<a href="#">Late Cycle Pre-Meeting</a> July 9, 2013
Send Briefing Packages to GE	July 17, 2013	By July 12, 2013[Fri.]
Issue DR Letters	July 21, 2013[Fri.]	
Late Cycle Meeting with GE	July 28, 2013	<a href="#">Late Cycle Meeting</a> July 23, 2013
Wrap Up Meeting	Sept. 7, 2013	Sept. 3, 2013 [Tues.]
OSI Clinical Inspection Summary Review	July 20, 2013	
Facility Inspections	(b) (4)	
Primary Review due to TL	Jun. 28, 2013 [Fri.]	
Secondary Review due to CDTL	July. 19, 2013 [Fri.]	
CDTL Review due to DD	Sept 20, 2013 [Fri.]	
Division Director Review	Oct. 4, 2013 [Fri.]	
<b>Month 12 Goal Date Standard, Office Sign-off</b>	<b>Oct. 25, 2013 [Fri.]</b>	
PDUFA Date	Oct. 26, 2013 [Sat.]	

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/s/  
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SHARON P THOMAS  
10/02/2013

## Wrap-up Meeting Minutes September 3, 2013

### NDA 203137 (PDUFA V- “Program”)

**Product:** Vizamyl (Flutemetamol F18 Injection)  
**Sponsor:** GE Healthcare  
**Proposed New Indication:** PET imaging for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment.

#### Team:

##### **Review Team for NDA 203137:**

- Libero (Louis) Marzella, M.D., Ph.D., Director (acting) DMIP
- Alex Gorovets, M.D., Deputy Director-
- Phillip Davis, M.D., Medical Officer
- Brenda Ye, M.D., Medical (TL and CDTL)
- Lan Huang, Ph.D., Statistics
- Jyoti Zalkikar, Ph.D., Statistics (TL)
- Sally Hargus, Ph.D., Non-Clinical
- Adebayo Lanionu, Ph.D., Non-Clinical (TL)
- Ravindra Kasliwal Ph.D., CMC
- Eldon Leutzinger, Ph.D., CMC (TL)
- Robert Mello, Ph.D., Micro
- Bryan Riley, Ph.D., Micro TL
- Sharon Thomas, (RPM)

#### Dates That Signed Reviews Are Due:

	<b>PDUFA- October 26, 2013</b>
<b>CDTL</b>	September 20, 2013
<b>Division Director Review</b>	October 4, 2013
<b>Office Director Review</b>	October 25, 2013

#### **1. Discipline Specific Reviews of Application**

- Conclusions of the studies/information submitted.  
*Discussion: Team recommends Approval. Efficacy studies met primary endpoints, Acceptable reading methodology and reader's performance, No safety issue. Stats verified primary efficacy analyses data.*
- Outstanding issues-
  - ❖ Clinical-None
  - ❖ CMC – None
  - ❖ P/T – None
  - ❖ Clin Pharm- None
  - ❖ Clinical (CDTL) – None
  - ❖ Stats – None
  - ❖ Micro- None
  - ❖ Consults –Inspections- *Acceptable*
  - ❖ Labeling –*Sent to sponsor on 8/30/13. RPM requested sponsor to send final labeling by Thurs., 9/5/13.*

*Discussion: There is one manufacturing site (Cardinal Health –Dallas) still pending. RPM will contact SEALD for End-of-Cycle review.*

#### **2. Signed Review Status**

- Primary Reviews: *Complete*
- Consult Reviews: *Complete*

## Wrap-up Meeting Minutes September 3, 2013

- CDTL: *Outstanding*
- Div Director Review: *Outstanding*

**Discussion:** *The Primary reviews and Consults are complete. The CDTL and Div. Director' will complete and submit reviews in DARRTS on 9/16/13.*

### 3. Outstanding REMS/PMR/PMC issues

- *None.*

### 4. Discussion of Proposed Action To Be Taken

- *Approval*
- *Target Action Date- October 25, 2013*
- *Press Release- Yes.*

MILESTONES	MILESTONE DEADLINES	MEETINGS
Receipt Date	October 26, 2012	
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Secondary Review due to CDTL	July. 19, 2013 [Fri.]	
CDTL Review due to DD	Sept 20, 2013 [Fri.]	
Division Director Review	Oct. 4, 2013 [Fri.]	
Office Director	Oct. 25, 2013[Fri.]	
<b>12 Month Goal Date Standard, Office Sign-off</b>	<b>Oct. 25, 2013 [Fri.]</b>	
PDUFA Date	Oct. 26, 2013 [Sat.]	

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/s/  
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SHARON P THOMAS  
09/16/2013

**From:** Thomas, Sharon [<mailto:Sharon.Thomas@fda.hhs.gov>]  
**Sent:** Monday, August 05, 2013 11:36 PM  
**To:** Clark, Paula (GE Healthcare)  
**Subject:** NDA 203137 Vizamyl - Labeling Discussion Comments

## **LABELING DISCUSSION COMMENTS**

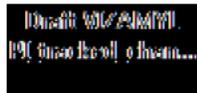
GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Paula:

Please refer to your pending NDA 203137 for Vizamyl™ and your July 12, 2013, email submission containing labeling revisions.

Attached is the FDA's edits to the PI. Please address the comments/edits and re-submit the label ( in track changes and MS Word versions) along with a commentary/justification document via e-mail by 10:00 am -Thursday, August 8, 2013.

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



Sincerely,  
Sharon

Sharon Thomas, B.Sc., RHIT, CCRP  
Regulatory Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
(301) 796-1994 (office)  
(301) 796-9849 (fax)  
[sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

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/s/  
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SHARON P THOMAS  
08/06/2013

# MEETING MINUTES

## Team-Labeling Meeting

**June 24, 2013**  
**NDA 203137**

### Vizamyl (Flutemetamol F 18 Injection)

---

**Submission Date:** October 26, 2012

**Proposed Indication:** PET imaging for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment.

**Meeting Purpose:** To discuss review discipline specific updates and finalize labeling.

**Review Status:**

- Standard Review requested (PDUFA V --- 12 month review) /October 26, 2013

**Team:** Libero Marzella, Phillip Davis, Jyoti Zalkikar, Gene Williams, Christy John, Sally Hargus, Adebayo Laniyonu, Ravindra Kasliwal, Mike Kieffer.

**SEALD:** Eric Brodosky

**Discussion points:**

1. **SEALD** - Eric Brodosky discussed specific labeling recommendations for the Vizamyl PI.
2. **RPM**- Discussed items to include in LCM briefing package. The team confirmed that there is not a need for PMCs or PMRs.
3. **CMC reviewer** – Will have comments/deficiencies in Primary Review to convey to GE
4. **RPM**- Reminded Team of Upcoming Milestones

MILESTONES	MILESTONE DEADLINES	MEETINGS
Receipt Date	October 26, 2012	
Day 45	December 10, 2012	<a href="#">Filing/Planning Meeting Dec. 3</a>
Day 60 (Filing Date)	December 24, 2012	
Day 74 Letter Due	January 8, 2013	

NDA 203137 – Team Mtg. /Mid-cycle Practice

Page 2

Team Meeting		Jan. 24, 2013 [Thurs.]
Team /Mid-Cycle Practice #1		Feb 19, 2013 [Tues.]
Team /Mid-Cycle Practice #2		March 7, 2013 [Thurs.]
Month 5- Mid-cycle	March 25, 2013	Mid-cycle Meeting <b>March 19</b>
Mid-cycle –Communication Mtg	April 9, 2013	Mid-cycle Communication Mtg <b>April 2</b>
Labeling Meetings		<b>Apr. 9, 2013 [Tues.]</b>
		<b>April 23, 2013 [Tues.]</b>
		<b>May 7, 2013 [Tues.]</b>
		<b>May 21, 2013 [Tues.]</b>
		<b>June 6, 2013 [Thurs.]</b>
Send Labeling to GE	July 8, 2013	
Late Cycle Pre-Meeting	July 14, 2013	Late Cycle Pre-Meeting <b>July 9, 2013</b>
Send Briefing Packages to GE	July 17, 2013	By July 12, 2013[Fri.]
Issue DR Letters	July 21, 2013[Fri.]	
Late Cycle Tcon with GE	July 28, 2013	Late Cycle SponTcon <b>July 23, 2013</b>
Wrap Up Meeting	Sept. 7, 2013	Sept. 3, 2013 [Tues.]
OSI Clinical Inspection Summary Review	July 20, 2013	
Facility Inspections	(b) (4)	
<b>OSE Review</b>	<b>Jun. 28, 2013 [Fri.]</b>	
Primary Review due to TL	Jun. 28, 2013 [Fri.]	
Secondary Review due to CDTL	July. 5, 2013 [Fri.]	
<b>DRISK Review/Memo</b>	<b>July 8, 2013 [Wed.]</b>	
CDTL Review due to DD	Sept 20, 2013 [Fri.]	
Division Director Review	Oct. 4, 2013 [Fri.]	
<b>Month 12 Goal Date Standard, Office Sign-off</b>	<b>Oct. 25, 2013 [Fri.]</b>	

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/s/  
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SHARON P THOMAS  
07/01/2013



NDA 203137

**DISCIPLINE REVIEW LETTER**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

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

We also refer to your amendments dated January 25, 2013, January 30, 2013, February 8, 2013, April 5, 2013 and March 14, 2013,

We have reviewed the Chemistry, Manufacturing, and Controls section of your submission and have identified the following deficiencies:

1. In the post approval stability protocol for Flutemetamol F18 Injection, you have indicated that the summary of the data generated will be written and maintained. This summary will be subjected to periodic review. Such stability data should also be reported in the annual report of the NDA to the NDA file. Provide amended stability protocol and commitment that indicates this.
2. The method for the determination of Flutemetamol is not sufficiently specific in that the flutemetamol peak is not resolved from the specified impurity (b)(4). Hence flutemetamol is quantified along with impurity (b)(4) and reported as such. Provide commitment that within 1 year of the date of approval of this New Drug Application you will submit method(s) that can specifically quantify flutemetamol and the (b)(4) impurity. You will also amend the finished product specifications to provide for acceptance criteria for flutemetamol amount and for (b)(4) impurity amount.
3. Revise the drug product vial labels (10 mL and 30 mL) to include the following:
  - Revise the proposed proprietary name throughout the labels and labeling to title case (i.e., Vizamyl).
  - Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence

commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).

- Place strength statement [REDACTED] (b) (4) below the established name (Flutemetamol F18 Injection) on the label.
- Relocate statement “Diagnostic – For intravenous use only” below the strength statement.
- Delete wording [REDACTED] [REDACTED] (b) (4) from storage statement.

4. Revise the carton (shield) labels to include the following:

- Revise the proposed proprietary name throughout the labels and labeling to title case (i.e., VizamyI).
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
- Relocate statement “Diagnostic – For intravenous use only” below the strength statement.
- Delete wording [REDACTED] [REDACTED] (b) (4) from storage statement

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at (301) 796-3908.

Sincerely,

*{See appended electronic signature page}*

Danae Christodoulou, Ph.D.  
Acting Chief, Branch 7, Division 3  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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DANAE D CHRISTODOULOU  
07/01/2013



NDA 203137

**LABELING DISCUSSION COMMENTS**

GE Healthcare Inc.  
Attention: Kevin D. White, MBA, RAC  
Senior Director and  
Americas Head, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Mr. White:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vizamyl™ (Flutemetamol F 18 Injection) 150 MBq/ML per multi-dose vial.

We also refer to our January 2, 2013, letter in which we notified you of our target date of July 8, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.”

Please find enclosed the revised Label for Vizamyl. Please provide GE’s proposed modifications along with commentary/rationale by COB on Monday, July 8, 2013. Please submit the label in track changes and clean MS Word versions via e-mail along with a formal NDA amendment submission.

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

Sincerely,

*{ See appended electronic signature page }*

Sharon Thomas, B.Sc., RHIT, CCRP  
Regulatory Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

ENCLOSURE: Draft Labeling

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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SHARON P THOMAS  
06/28/2013

**From:** Thomas, Sharon  
**Sent:** Monday, June 17, 2013 12:53 PM  
**To:** Clark, Paula (GE Healthcare) ([Paula.Clark@ge.com](mailto:Paula.Clark@ge.com))  
**Cc:** 'kevin.d.white@ge.com'  
**Subject:** CMC Information Request: NDA 203137/ flutemetamol

## INFORMATION REQUEST

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vizamyl, flutemetamol (NDA 203137) submitted and received October 26, 2012. We have the following chemistry comments and information requests:

- 1. You have not updated the NDA application file to reflect changes (e.g., specifications and methods) proposed in 20-May-2013. Provide update to the NDA application file that reflects changes proposed in the 20-May-2013 amendment.**
- 2. In the method described for total content of Polysorbate 80 and related substances in the formulation buffer, describe the NIR software that is used and was validated, and clarify the specified range and Mahalanobis distance for acceptable results.**
- 3. Provide an update to the stability of “formulation buffer” solution.**
- 4. In the method for determination of the identity of [<sup>18</sup>F]flutemetamol, the total content of flutemetamol and related substances and the radiochemical purity (RCP) of Flutemetamol F18 Injection by HPLC, you have not provided validation data for accuracy for the radioactivity detector. It is not clear if the HPLC would retain free <sup>18</sup>F-fluoride, if present. Provide data to support that the HPLC does not retain free <sup>18</sup>F-fluoride. Also, indicate where would free <sup>18</sup>F-fluoride elute in the radioactivity chromatogram.**

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 **12PM, Wednesday, June 19, 2013**, and then follow up with a formal amendment to the NDA.

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

Best regards,

Sharon Thomas, RPM  
Division of Medical Imaging Products  
(301) 796-1994 (office)

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/s/  
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SHARON P THOMAS  
06/17/2013

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**From:** Thomas, Sharon  
**Sent:** Thursday, May 09, 2013 12:56 PM  
**To:** 'Clark, Paula (GE Healthcare)'  
**Subject:** NDA 203137/Vizamyl/Pharmtox- Information Request

## **INFORMATION REQUEST**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for Vizamyl (NDA 203137) submitted and received October 26, 2012. We have the following comments and information requests:

### **Regarding Study B067017:**

Please clarify the maximum dose administered to rats in Study B067017. We note that other **nonclinical in vivo** studies conducted during the same time period with the same Test Article formulation of Flutemetamol (7% ethanol in PBS) required a downward adjustment of the nominal administered dose, due to flutemetamol adsorption to infusion equipment. If the stated maximum dose of [REDACTED] <sup>(b)(4)</sup> is correct, please explain how the administered dose was verified.

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 12PM, Monday, May 13, 2013, and then follow up with a formal amendment to the NDA.

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

Best regards,  
Sharon Thomas, RPM  
Division of Medical Imaging Products  
(301) 796-1994 (office)

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/s/  
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SHARON P THOMAS  
05/09/2013

**From:** Davis-Warren, Alberta E  
**To:** ["Clark, Paula \(GE Healthcare\)"](#)  
**Cc:** [Thomas, Sharon](#)  
**Subject:** RE: NDA 203137/Flutemetamol/ SAS dataset information request  
**Date:** Tuesday, April 02, 2013 3:26:00 PM

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Dear Ms. Clark,

Please see the following information request regarding the SAS dataset:

Reference is made to our March 22, 2013 FDA Information Request, and the GE Healthcare response to our information request submitted to the Agency by email on March 29, 2013.

We have the following additional requests related to the following abbreviations contained with the SAS dataset table, seen in the last column on the right:

1. Please confirm that "SOTTYP" is an abbreviation for "Standard of Truth Type".
2. Define "BSS".
3. Define "Presum".

Please respond to the information request by no later than Friday, April 5, 2013 at 4 pm EDT. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail ([Alberta.Davis-Warren@fda.hhs.gov](mailto:Alberta.Davis-Warren@fda.hhs.gov)) no later than Friday, April 5, 2013 at 4 pm EDT.

Please contact me if you have any questions.

Thank you,  
Alberta

Alberta E. Davis-Warren  
Regulatory Health Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
301-796-3908 office  
301-796-9849 fax  
[Alberta.Davis-Warren@fda.hhs.gov](mailto:Alberta.Davis-Warren@fda.hhs.gov)

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**From:** Clark, Paula (GE Healthcare) [<mailto:Paula.Clark@ge.com>]  
**Sent:** Friday, March 29, 2013 12:27 PM  
**To:** Davis-Warren, Alberta E  
**Cc:** Thomas, Sharon  
**Subject:** NDA 203137/Flutemetamol/ Information Request/ Mid-Cycle Communication Meeting

Dear Ms. Davis-Warren:

Reference is made to the April 2, 2013 FDA Mid-cycle Review Meeting for NDA 203137. Further reference is made to the CMC and Statistical Information Request received from FDA on March 22 in the email message below.

As requested by the agency, we are providing our responses, including the attached sas dataset, today, March 29, 2013, via email. The same response documents will be formally submitted to NDA

203137.

Can you please confirm that the sas dataset was received, and also, please confirm that the reviewer was able to easily open and read the dataset?

Finally, as agreed we will not be using the FDA dial-in information provided in the email below, but will use GE Healthcare's dial-in information submitted to you yesterday.

Please do not hesitate to contact me with any further questions or comments. If you need to reach me by telephone today, please call me at 609 917 5815.

Best regards,

*Paula Clark, RAC*  
*GE Healthcare*  
*Global Regulatory Lead, Flutemetamol*  
*T 609 514 6883*  
*F 609 228 6198*

(b) (6)

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**From:** Thomas, Sharon [<mailto:Sharon.Thomas@fda.hhs.gov>]  
**Sent:** Friday, March 22, 2013 10:39 AM  
**To:** Clark, Paula (GE Healthcare)  
**Cc:** Davis-Warren, Alberta E  
**Subject:** NDA 203137/Flutemetamol/ Information Request/ Mid-Cycle Communication Meeting

Dear Ms. Clark,

Attached, please find a CMC and Statistical Information Request for Flutemetamol. The Division would like GE to address these items during the Mid-cycle Communication Meeting. I will be out of the office on April 2<sup>nd</sup>, however Ms. Davis Warren has graciously agreed to cover the meeting in my absence so please remember to cc her on all communication. I have provided the meeting details below including the FDA's list of attendees. Please don't hesitate to contact me if you have any questions.

Best regards,

*Sharon*

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

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

**Mid-Cycle Communication Meeting**

**Teleconference:** Tuesday, April 2, 2013 11:00 am- 12:00 pm EST

Call in Numbers:

(b) (6)

International:



**FDA's Participants:**

- Rafel Rieves, MD, Director, Division of Medical Imaging Products (DMIP)
- Libero Marzella, MD, Deputy, Division Director, DMIP
- Alex Gorovets, MD, Clinical Team Leader, DMIP
- Lucie Yang, MD, PhD, Primary Medical Team Leader, DMIP
- Phillip Davis, MD, Primary Reviewer, DMIP
- Ravindra Kasliwal, PhD, Clinical Reviewer, ONDQA
- Robert Mello, PhD, Microbiologist, OPS/NDMS
- Jyoti Zalkikar, PhD, Statistical Team Leader, DMIP
- Lan Huang, PhD, Statistical Reviewer, DMIP
- Sally Hargus, PhD, Pharm/Tox Reviewer, DMIP
- Adebayo Lanijonu PhD, Pharm/Tox , Team Leader, DMIP
- Gene Williams, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCP5
- Christy John, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCP5
- Alberta Davis-Warren, BSc, Sr., Regulatory Project Manager, DMIP

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/s/  
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ALBERTA E DAVIS WARREN  
04/02/2013



**NDA 203-137**

**INFORMATION REQUEST**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

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

We are reviewing the Chemistry Manufacturing and Controls (CMC) and Statistical sections of your submission and have the following comments and information requests:

CMC

1. Your proposed specifications for Flutemetamol F18 Injection drug product control the “total Content of Flutemetamol and related impurities” together. You need to quantify flutemetamol content separately from the related impurities content. The flutemetamol content will need to be specified in the labeling and needs to be supported by specification. Provide revised specifications for Flutemetamol F18 injection that include separate specifications for flutemetamol and for related impurities. Provide justifications for the proposed acceptance criteria for these as well as updated analytical procedure(s).
2. [Redacted] (b) (4)
3. Your specifications for [Redacted] (b) (4) do not include specification for [Redacted] (b) (4) content (impurity). Include specification for [Redacted] (b) (4) content as part of your company’s specification for [Redacted] (b) (4). Provide updated specifications for [Redacted] (b) (4).
4. [Redacted] (b) (4)

STATISTICAL

5. The current efficacy data for Study 021 only includes some dummy grouping variables (such as studygr1, studygr2, ...studyg12). Please provide a sas data set that includes the unique subject identification number (usubjid) and clinical diagnosis for all the 276 subjects in study 021.
  - a. The clinical diagnosis should be one variable with values such as normal, AD, MCI, ...etc. This will be necessary for subgroup analyses by clinical diagnosis.
  - b. Please provide the clinical diagnosis information for the subjects with a standard of truth (autopsy and biopsy) in the same sas data set.

Please address the above items at the Mid-cycle Communication Meeting on April 2, 2013 and follow-up with a formal response after the meeting. 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

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/s/  
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RAFEL D RIEVES  
03/22/2013

**From:** Thomas, Sharon  
**Sent:** Friday, March 15, 2013 8:29 AM  
**To:** Clark, Paula (GE Healthcare) (Paula.Clark@ge.com)  
**Subject:** NDA 203137 - Clinical Information Request

**March 15, 2013**

## **INFORMATION REQUEST**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for Vizamyl (NDA 203137) submitted and received October 26, 2012. We have the following comments and information requests:

1. Please provide transcripts of the DVD reader training program and the technologist training program (for reorienting images) for study GE067-021. If these documents exist in the NDA, please provide the location.
2. We note that the independent review charter link (in the study report body) for study GE067-015 is to a document in the GE067-005 study files titled "Independent Review Charter GE-067-005". Please clarify if the independent review charter for studies GE067-015 and GE067-005 are one and the same document. If there is a separate, unique independent review charter for study GE067-015, please submit this document or provide the location of the document in the NDA.
3. Regarding study GE067-015, we note the study report synopsis states the following:

"All scans from this study were blindly and randomly mixed with **approximately equal numbers** of [18F] flutemetamol scans from the GE-067-005 mild cognitive impairment study (which was expected to contain some abnormal images) to avoid potential bias if readers saw only (or predominantly) normal scans."

In the statistical analysis plan for study GE067-015, it is stated on page 20 of 34 that:  
"All scans from this study will be blindly and randomly mixed with abnormal scans (**approximately 100 scans**) from previously read [18F] flutemetamol PET images to avoid biases in the evaluation of potentially normal scans."

Please

- a. provide the total number of “mixed in” scans from previously read flutemetamol PET images that were mixed with GE067-015 scans for the primary efficacy analysis reads;
- b. confirm from which study(ies) these “mixed-in” scans originated;
- c. provide a table showing, by reader, the final interpretation (normal or abnormal) for all study GE067-015 “mixed-in” scans. If this information exists in the NDA, please supply the location.

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 12PM, Thursday, March 21, 2013, and then follow up with a formal amendment to the NDA.

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

Best regards,  
Sharon Thomas, RPM  
Division of Medical Imaging Products  
(301) 796-1994 (office)

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/s/  
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SHARON P THOMAS  
03/15/2013

**From:** Thomas, Sharon  
**Sent:** Monday, March 11, 2013 11:45 AM  
**To:** Clark, Paula (GE Healthcare)  
**Cc:** 'Longenecker, Fred (GE Healthcare)'  
**Subject:** NDA 203137 - Flutemetamol F18 Injection - Clinical/Statistical Information Request

Dear Ms. Clark,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flutemetamol. We have the following comments and information requests:

- Please provide a listing of clinical diagnosis (e.g. Mild Cognitive Impairment, Alzheimer's Disease, normal cognition, other dementia) for each autopsy subject (by subject number) and for each subject who underwent brain biopsy for determination of amyloid status (by subject number). Please also provide the truth standard result for each subject in this table. If this information has been provided to NDA 203137, please provide the submission date and location.

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 12PM, Thursday, March 14, 2013, and then follow up with a formal amendment to the NDA.

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

Best regards,  
Sharon Thomas, RPM  
Division of Medical Imaging Products  
(301) 796-1994 (office)

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/s/  
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SHARON P THOMAS  
03/11/2013

**From:** Thomas, Sharon  
**Sent:** Friday, March 01, 2013 2:08 PM  
**To:** Clark, Paula (GE Healthcare) (Paula.Clark@ge.com)  
**Subject:** NDA 203137 / Vizamyl (flutemetamol)- Information Request

## INFORMATION REQUEST

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

We acknowledge the receipt of your new drug application for Vizamyl (NDA 203137) submitted and received October 26, 2012. We have the following comments and information requests:

1. Please provide a single dataset containing all of the raw data from the analytical runs for all samples contributing to PK analysis. The file should include (each item is a column):
  - a. Clinical study number
  - b. Calendar date of analysis of the sample ("sample" includes blanks, standards, QCs – all determinations included in the analytical run)
  - c. Clock time of analysis of the sample
  - d. Categorical variable describing sample type --blank, standard, QC, subject data, re-analysis, dilution
  - e. For subject data only (column is empty for non-subject samples) -- subject ID, nominal post-dose sample time, actual post-dose sample time (these could be split into separate columns if desired)
  - f. For subject data only (column is empty for non-subject samples and for samples that are not dilutions) -- the degree (x-fold) of dilution
  - g. (and subsequent) Other information as you desire to include
2. Is there an explanation for the finding that the estimated terminal half-life for [18F]flutemetamol exceeds the physical half-life of [18F]?
3. Please provide a comparative assessment of the performance of SUVR vs. visual read, relative to the standard of truth, for all readers (5 or 3, as appropriate) for all studies.
4. Are *in vitro* metabolism studies available from either GE or from the scientific literature?

In the interest of time, please provide a response by e-mail to my attention:  
[sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by 12:00 PM, Friday, March 8, 2013.

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

Sincerely,

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  
03/01/2013

**From:** Thomas, Sharon  
**Sent:** Wednesday, February 27, 2013 4:29 PM  
**To:** Clark, Paula (GE Healthcare) (Paula.Clark@ge.com)  
**Subject:** NDA 203137 / Vizamyl (flutemetamol)- Information Request

## **INFORMATION REQUEST**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

We acknowledge the receipt of your new drug application for Vizamyl (NDA 203137) submitted and received October 26, 2012. We have the following comments and information requests regarding GE067-007:

1. Upon initial review of the application, we cannot locate a description of how the pathology regional mean cutoff of 1.5 was chosen and when it was selected. To assist us in our clinical review, please direct us to the section of the application that explains this. Alternatively, provide a detailed justification for the 1.5 cutoff and clearly explain when it was chosen.

In the interest of time, please provide a response by e-mail to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by 12:00 PM, Wednesday, March 6, 2013.

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

Sincerely,

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  
02/27/2013



NDA 203137

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

GE Healthcare  
101 Carnegie Center  
Princeton, NJ 08540

ATTENTION: Paula M. Clark, RAC  
Senior Manager, Regulatory Affairs

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted and received October 26, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Flutemetamol Injection, 185 MBq/mL.

We also refer to your correspondence, dated and received November 20, 2012, requesting review of your proposed proprietary name, Vizamyl. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Vizamyl, 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.

Additionally, if **any** of the proposed product characteristics as stated in your November 20, 2012, 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 Rimmel, 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}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
02/14/2013

**TEAM MEETING #1**  
**Meeting Minutes**  
**January 24, 2013**  
**NDA 203137**

**Vizamyl (Flutemetamol F 18 Injection)**

---

**Submission Date:** October 26, 2012  
**PDUFA Date:** October 26, 2013

**Proposed Indication:** PET imaging for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment.

**Meeting Purpose:** To discuss review discipline specific updates and to prepare for the upcoming mid-cycle meeting.

**Review Team:**

Rafel Rieves, M.D., Director DMIP- *Present*  
Lucie Yang, M.D., Clinical Team Leader, (TL& CDTL) *Present*  
Philip Davis, M.D, Medical Officer, *Present*  
Sally Hargus, Ph.D, Non-Clinical, *Present*  
Lan Huang, Ph.D., Statistics, *Present*  
Jyoti Zalkikar, Ph.D., Statistics (TL) *Present*  
Christy John, Ph.D., Clinical Pharmacology *Present*  
Ravindra Kasliwal, Ph.D, CMC *Present*  
Bob Mello, Ph.D., Microbiology, *Present*  
Yelena Maslov, OSE, TL *Present*  
Sandra Rimmel, OSE, Project Manager, *Present*

**1. Review Discipline Updates**

Clinical - **DISCUSSION DURING MEETING:** Review is on-going. Preparations for the mid-cycle presentation are underway.

Nonclinical- **DISCUSSION DURING MEETING:** There are no P/T issues at this stage--the NDA is under review. Reviewer is on track at this point to meet the PDUFA goals. Reviewer will present a brief summary of the P/T review, highlighting P/T concerns (if any).

Statistics- **DISCUSSION DURING MEETING:** Reviewer checked study 007 (autopsy study) and 021 (healthy subjects). Do not have any stat issues at this point. Reviewer will check the pooled reading study later and present a summary in the mid cycle meeting.

Microbiology- **DISCUSSION DURING MEETING:** Review is on-going- Reviewer will meet the PDUFA goals. Reviewer requested that CMC follow-up with sponsor to obtain filter integrity testing.

CMC- **DISCUSSION DURING MEETING:** Review is on-going. Reviewer noted that sponsor did not formally respond to the December 7, 2012 CMC information request concerning filter integrity testing. RPM to follow-up with sponsor.

OSE/Safety- **DISCUSSION DURING MEETING:** No safety concerns at this point- Confirmed that the proposed proprietary name, Vizamyl is acceptable.

OSI- **DISCUSSION DURING MEETING:** None of the five inspections have been completed to date but all are expected to be completed well before July 26, the inspection summary goal date.

**2. Preparation for upcoming Mid-Cycle Meeting in March:**

Presentations (who will/will not be presenting at the mid-cycle meeting)

- Clinical-
- Statistical-
- Clinical Pharmacology-
- Non-Clinical-
- CMC-
- Micro-

**DISCUSSION DURING MEETING:** There will be formal presentations from clinical, statistical, clinical pharmacology, non-clinical and CMC. Micro will not present.

**3. Milestones/Upcoming Meetings:**

MILESTONES	MILESTONE DEADLINES	MEETINGS
Receipt Date	October 26, 2012	
Day 45	December 10, 2012	<a href="#">Filing/Planning Meeting</a> Dec. 3
Day 60 (Filing Date)	December 24, 2012	
Day 74 Letter Due	January 8, 2013	
Team Meeting		Jan. 24, 2013 [Thurs.]
Team /Mid-Cycle Practice #1		Feb 19, 2013 [Tues.]
Team /Mid-Cycle Practice #2		March 7, 2013 [Thurs.]
Month 5- Mid-cycle	March 25, 2013	<a href="#">Mid-cycle Meeting</a> March 19
Mid-cycle –Communication Mtg	April 9, 2013	<a href="#">Mid-cycle Communication Mtg</a> April 2
Labeling Meetings		Apr. 9, 2013 [Tues.]
		April 23, 2013 [Tues.]
		May 7, 2013 [Tues.]
		May 21, 2013 [Tues.]

		June 6, 2013 [Thurs.]
Send Labeling to GE	July 8, 2013	
Late Cycle Pre-Meeting	July 14, 2013	<a href="#">Late Cycle Pre-Meeting</a> July 9, 2013
Send Briefing Packages to GE	July 17, 2013	By July 12, 2013[Fri.]
Issue DR Letters	July 21, 2013[Fri.]	
Late Cycle Tcon with GE	July 28, 2013	<a href="#">Late Cycle SponTcon</a> July 23, 2013
Wrap Up Meeting	Sept. 7, 2013	Sept. 3, 2013 [Tues.]
OSI Clinical Inspection Summary Review	July 26, 2013	
Facility Inspections	(b) (4)	
Primary Review due to TL	Jun. 28, 2013 [Fri.]	
Secondary Review due to CDTL	July. 19, 2013 [Fri.]	
CDTL Review due to DD	Sept 20, 2013 [Fri.]	
Division Director Review	Oct. 4, 2013 [Fri.]	
<b>Month 12 Goal Date Standard, Office Sign-off</b>	<b>Oct. 25, 2013 [Fri.]</b>	

**DISCUSSION DURING MEETING:** RPM discussed upcoming milestones. No discussion during the meeting occurred regarding the timelines noted above.

4. **Other items:**
  - PeRC scheduled for May 8th.

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/s/  
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SHARON P THOMAS  
01/24/2013

**From:** Thomas, Sharon  
**Sent:** Wednesday, December 12, 2012 1:06 PM  
**To:** Clark, Paula (GE Healthcare) (Paula.Clark@ge.com)  
**Subject:** NDA 203137 - Clinical Information Request

## **INFORMATION REQUEST**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

We acknowledge the receipt of your new drug application for Vizamyl (NDA 203137) submitted and received October 26, 2012. We have the following comments and information requests regarding GE067-007.

On page 311 of 417 in the independent review charter appendix of the study report for GE067-007 (5.3.5.1.3, section 16.1.1), the document states the following:

“The BIE will be prepared and conducted by staff of the Sponsor’s Image Review Centre (IRC), a group that is part of GE Healthcare Medical Diagnostics R&D, which will act as the core laboratory for the BIE. The reader training and [image evaluation](#) will take place at The Grove Centre in the U.K.”

On page 386 (under "Definitions"), this document then states:

“GE Healthcare (GEHC) Image Review Center (IRC): GE facility based in Oslo, Norway responsible for setting up Medstamp, image transfer, quality control checking of the data, archiving of images and [blinded reads](#).”

Please clarify all sites where the blinded, independent image reads were conducted for study GE067-007, including the numbers of reads conducted at each site. Additionally, please clarify where the source documents used by image readers to document the final interpretations are stored for study GE067-007. If these documents are stored at multiple sites, please provide all sites and complete contact information (name, address, phone, fax, email) for each site.

In the interest of time, please provide a response by e-mail to my attention: sharon.thomas @fda.hhs.gov, by 12:00 PM, Friday, December 14, 2012.

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

Sincerely,

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  
12/12/2012

**FILING MEETING MINUTES**  
**December 3, 2012**  
New NDA 203137

**Vizamyl (Flutemetamol F 18 Injection)**

---

**Submission Date:** October 26, 2012

**Received Date:** October 26, 2012

**Proposed Indication:** PET imaging for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment.

**Current Review Team for NDA 203137:**

Charley Ganley, M.D., Director, ODE IV-*Present*

Rafel Rieves, M.D., Director DMIP-*Present*

Louis Marzella, M.D. Ph.D., Dep. Director DMIP- *Present*

Sharon Thomas., Regulatory Health Project Manager -*Present*

Kaye Kang (CPMS)

Phillip Davis, M.D., Medical Officer -*Present*

Lucie Yang, M.D., Ph.D . (TL and CDTL)-*Present*

Lan Huang, Ph.D., Statistics -*Present*

Jyoti Zalkikar, Ph.D., Statistics (TL) -*Present*

Christy John, Ph.D., Clinical Pharmacology-*Present*

Gene Williams, Ph.D, Clinical Pharmacology (TL)--*Present*

Sally Hargus, Ph.D., Non-Clinical-*Present*

Adebayo Lanionu, Ph.D., Non-Clinical (TL) -*Present*

Ravindra Kasliwal, Ph.D., Product-*Present*

Ali Al Hakim, Ph.D., Product (TL)

Bob Mello, Ph.D. Microbiology Reviewer-*Present*

Bryan Riley, Ph.D. Microbiology (TL)

**Additional Attendees:**

Alex Gorovets, MD/ DMIP

Sandra Rimmel/ OSE

Mike Kiefer/ OSE

Yelene Maslov/ OSE

Jim Dvorsky, James OPDP

**Agenda Items and Discussion:**

**1. Review Status:**

Standard Review (PDUFA V --- 12 month review)

User Fee Paid

Categorical Exclusion from environmental assessment requested

Requested full waiver of pediatric studies

Requested waiver of carcinogenicity studies

**DISCUSSION:** Standard review confirmed. RPM will send pediatric waiver information to PeRC. RPM will submit consult to SEALD. No need for Maternal Health, Peds or Neurology consults. No AC meeting.

**Agenda Items:**

1. **Discuss Filing Issues by Primary Discipline**

Clinical

**Comments:** The submission is fileable.

The sponsor to respond on Wed., 12/5/12, to the clinical sites- information request.

Nonclinical

**Comments:** The application is fileable.

Statistics

**Comments:** No issues. - Application is fileable.

Clinical Pharmacology

**Comments:** May address QT concerns at NDA Orientation Meeting.

Microbiology

**Comments:** The submission is fileable.

Details of the sterility and bacterial endotoxins test methods were lacking in that there was only a simple reference to USP <71> and <85>, respectively. The following information request will be conveyed to the applicant. Please provide the following additional information:

- A description of the bacterial endotoxins test method to include relevant assay qualification data as well as the determination of the Maximum Valid Dilution, the routine sample dilution and the sensitivity of the test.
- A description of the sterility test method to include the media used, sample volume and incubation conditions. Does sampling for sterility (and endotoxins) occur before or after the saline (tonicity adjustment) addition? Also, describe the controls that are in place which assure the adequacy of the growth media.

CMC

**Comments:** The application is filable.

- We noted that the final intermediate AH11907 content in the cassette vial containing (b) (4) AH11907 in DMSO is determined by infrared spectroscopy in combination with multivariate statistical calibration. The control of material section does not provide the details of the method, including complete details of validation and the multivariate analysis performed. Provide full details of the method including the details of multivariate analysis performed and how results are calculated along with validation data.
- The infrared spectroscopy method for the determination of final intermediate AH11907 content in the cassette vial containing (b) (4) AH11907 in DMSO seems to be calculating the combined AH11907 content and content of related substances. This appears to indicate a lack of specificity of the content method. Clarify this apparent lack of specificity of the method, its effect on drug product quality and why the HPLC method used to determine impurities (b) (4) and related substances) may not be used to assay the content of AH11907 in DMSO.
- Provide the container closure and stability information, data and proposed expiration dating period for AH11907 in DMSO vial provided in cassette.
- The impurity content [impurity (b) (4) by HPLC (NMT (b) (4) % area) and sum of unspecified impurities by HPLC (NMT (b) (4) % area)] in the AH11907 in DMSO vial provided in cassette do not appear to be similar to the impurities in (b) (4) powder. Clarify if the impurities and their content are similar or different. And, if the impurities present are purged / removed during the drug substance / drug product manufacture. Provide such data.
- Provide information and data on tonicity (osmolality) of the drug product solution.
- We noted that the formulation buffer vial is manufactured at GE Healthcare AS in Oslo, Norway and supplied to each drug product manufacturing site. Provide information on its manufacture, specifications, container closure and expiration dating period for the formulation buffer.
- We noted that the drug product manufacturers do not seem to perform (b) (4) integrity testing on the (b) (4) that is primarily used to (b) (4) the finished drug product as part of product release (specifications).

- Include testing for (b)(4) integrity specifications as part of the drug product release specifications.
- Clarify the osmolality of the drug product solution. Provide osmolality data on qualification batches of the drug product.
- Provide information on the type of closure (e.g., type of rubber formulation used) for each of the finished product vial, quantitative composition of the formulation, and information that the formulation meets the USP chapter <661>, USP chapter <87> and USP chapter <88>), and type of crimp seal used. You may provide reference to appropriate Drug Master File (DMF) from the closure supplier (b)(4) along with Letter (s) of authorization for us to review their DMF in support of your application.

**DISCUSSION:** The application is fileable. RPM will convey the above CMC and Micro comments in an Advice letter. Reminder was given to the team to submit their filing memos in DARRTS.

2. **Applicant Orientation Presentation:** December 13, 2012.

**DISCUSSION:** No discussion occurred.

3. **Milestones/Upcoming Meetings:**

MILESTONES	MILESTONE DEADLINES	MEETINGS
Receipt Date	October 26, 2012	
Day 45	December 10, 2012	<a href="#">Filing/Planning Meeting</a> Dec. 3
Day 60 (Filing Date)	December 24, 2012	
Day 74 Letter Due	January 8, 2013	
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Team /Mid-Cycle Practice #1		Feb 19, 2013 [Tues.]
Team /Mid-Cycle Practice #2		March 7, 2013 [Thurs.]
Month 5- Mid-cycle	March 25, 2013	<a href="#">Mid-cycle Meeting</a> March 19
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CDTL Review due to DD	Sept 20, 2013 [Fri.]	
Division Director Review	Oct. 4, 2013 [Fri.]	
Month 12 Goal Date Standard, Office Sign-off	Oct. 25, 2013 [Fri.]	

**DISCUSSION:** Reminder was given to the team regarding the milestone items/meetings noted above.

**4. Miscellaneous Items or Issues:**

- a. Any labeling concerns?

**DISCUSSION:** No labeling concerns.

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/s/  
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SHARON P THOMAS  
12/05/2012



**NDA 203137**

**INFORMATION REQUEST**

GE Healthcare Inc.  
Attention: Kevin D. White, MBA, RAC  
Senior Director and  
Americas Head, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Mr. White:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vizamyl™ (Flutemetamol F 18 Injection) 150 MBq/ML per multi-dose vial.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) and Microbiology sections of your submission and have the following comments and information requests:

CMC

1. We noted that the final intermediate AH11907 content in the cassette vial containing (b) (4) AH11907 in DMSO is determined by infrared spectroscopy in combination with multivariate statistical calibration. The control of material section does not provide the details of the method, including complete details of validation and the multivariate analysis performed. Provide full details of the method including the details of multivariate analysis performed and how results are calculated along with validation data.
2. The infrared spectroscopy method for the determination of final intermediate AH11907 content in the cassette vial containing (b) (4) AH11907 in DMSO seems to be calculating the combined AH11907 content and content of related substances. This appears to indicate a lack of specificity of the content method. Clarify this apparent lack of specificity of the method, its effect on drug product quality and why the HPLC method used to determine impurities ((b) (4) and related substances) may not be used to assay the content of AH11907 in DMSO.
3. Provide the container closure and stability information, data and proposed expiration dating period for AH11907 in DMSO vial provided in cassette.
4. The impurity content [impurity (b) (4) by HPLC (NMT (b) (4) % area) and sum of unspecified impurities by HPLC (NMT (b) (4) % area)] in the AH11907 in DMSO vial provided in cassette do not appear to be similar to the impurities in (b) (4) powder.

Clarify if the impurities and their content are similar or different. And, if the impurities present are purged / removed during the drug substance / drug product manufacture. Provide such data.

5. Provide information and data on tonicity (osmolality) of the drug product solution.
6. We noted that the formulation buffer vial is manufactured at GE Healthcare AS in Oslo, Norway and supplied to each drug product manufacturing site. Provide information on its manufacture, specifications, container closure and expiration dating period for the formulation buffer.
7. Include testing for [REDACTED] (b)(4) integrity specifications as part of the drug product release specifications.
8. Clarify the osmolality of the drug product solution. Provide osmolality data on qualification batches of the drug product.
9. Provide information on the type of closure (e.g., type of rubber formulation used) for each of the finished product vial, quantitative composition of the formulation, and information that the formulation meets the USP chapter <661>, USP chapter <87> and USP chapter <88>), and type of crimp seal used. You may provide reference to appropriate Drug Master File (DMF) from the closure supplier [REDACTED] (b)(4) [REDACTED] along with Letter (s) of authorization for us to review their DMF in support of your application.

#### Microbiology

10. Please provide a description of the bacterial endotoxins test method to include relevant assay qualification data as well as the determination of the Maximum Valid Dilution, the routine sample dilution and the sensitivity of the test.
11. A description of the sterility test method to include the media used, sample volume and incubation conditions. Does sampling for sterility (and endotoxins) occur before or after the saline (tonicity adjustment) addition? Also, describe the controls that are in place which assure the adequacy of the growth media.

In the interest of time, please provide a response by e-mail to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by 12:00 PM, Friday, December 7, 2012 along with a formal amendment to the NDA.

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

Sincerely,

*{See appended electronic signature page}*

Ali Al-Hakim, Ph.D.  
Branch VII Chief, ONDQA  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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/s/  
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ALI H AL HAKIM  
12/04/2012

**From:** Thomas, Sharon  
**Sent:** Saturday, December 01, 2012 3:10 PM  
**To:** Clark, Paula (GE Healthcare) (Paula.Clark@ge.com)  
**Subject:** NDA 203137- Information Request

## **INFORMATION REQUEST**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

We acknowledge the receipt of your new drug application for Vizamyl (NDA 203137) submitted and received October 26, 2012. We have begun our initial review and have the following comments and information requests.

1. It appears the “Clinical Sites for Inspection” document may contain inaccuracies with regards to the number of subjects screened and the number of protocol deviations, when compared to the protocol deviation listings document for studies GE 067-015 and GE 067-007. For example, on page 3 of 3 in the “Clinical Sites for Inspection” document (1.1.2) for study GE067-015, 42 subjects are stated to have been screened with 0 protocol deviations. However, in the “Protocol Deviation Listing” document (5.3.5.1.17) for study GE067-015, it appears there were 12 protocol deviations at this site. We note there are other examples of this type scenario in these documents for the pivotal studies. Please cross examine these documents for studies GE067-007, GE067-015 & GE067-021 and provide an accurate report of the number of subjects screened and enrolled, as well as the number of protocol deviations for each site in these pivotal studies.
2. Please confirm that the [REDACTED] (b) (4) was responsible for reader training and conducting the BIE for clinical study GE067-021. If this is not the case, please clarify where the BIE was performed for study GE067-021; include complete contact information with name, address, phone, and fax number.
3. Please confirm that the Grove Center was responsible for reader training and conducting the BIE for clinical study GE067-007. If this is not the case, please clarify where the BIE was performed for study GE067-007; include complete contact information with name, address, phone, and fax number.

4. Please clarify where the blinded image interpretations were performed for study GE067-015; include complete contact information with name, address, phone, and fax number.
5. Based on our initial review of document 16.1.1 (Protocol and Amendments) for study GE067-007, it appears that one histopathologist provided the truth standard read (Bielschowsky stain) for each brain tissue sample. Please confirm or correct our understanding of the number of readers for each subject's truth standard histopathology read. Please also clarify how many brain tissue samples were read by each histopathologist participating in the truth standard interpretations.

In the interest of time, please provide a response by e-mail to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by 12:00 PM, Wednesday, December 5, 2012 along with a formal amendment to the NDA.

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

Sincerely,

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  
12/01/2012



NDA 203137

**NDA ACKNOWLEDGMENT**

GE Healthcare Inc.  
Attention: Kevin D. White, MBA, RAC  
Senior Director and  
Americas Head, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Mr. White:

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: VIZAMYL™ (Flutemetamol F 18 Injection) 150 MBq/ML per multi-dose vial

Date of Application: October 26, 2012

Date of Receipt: October 26, 2012

Our Reference Number: NDA 203137

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 December 25, 2012, 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BSc, 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  
11/02/2012



IND 101,866

ADVICE/INFORMATION REQUEST

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [<sup>18</sup>F] Flutemetamol Injection.

We also refer you to your submissions dated February 11, 2011 and April 8, 2011.

We have reviewed the referenced material and have the following comments to your questions: Your questions are in *italic* and our responses are in **boldface**.

**FDA General Comments:**

- I. **We strongly disagree with your proposal to base your primary specificity determination solely on young healthy volunteers without histopathology. We strongly encourage continuation of the autopsy study in order to try to produce a subject-level sample size sufficient to reliably estimate sensitivity and specificity of the imaging test relative to the histopathology standard. We strongly advise continued efforts to obtain autopsy information throughout premarketing development. The basis for our concern is outlined below.**
  
- II. **We reviewed the protocols and associated documents for GE-067-007 and GE-067-015 in light of the discussions from the January 2011 advisory committee meeting. We have the following comments for you to consider as you further refine your plans. At the January 20, 2011 advisory committee discussion of another amyloid imaging agent, the following points were cited as especially important in the development of these types of products:**
  - a. **The image interpretation process for clinical (market) use of the drug needs to be established in premarket studies. We favour the use of training materials that do not necessitate person to person, on-site interaction with instructors (instead, we favour a computerized format). For example, a sponsor may choose to use a format (such as computerized training/DVD/CD) that provides the nuclear medicine physician with information necessary to accurately and reproducibly read the**

images without any need for “hands on” training and certification. We generally anticipate that training materials would be handled by FDA in a manner similar to other marketing materials in the post-approval setting.

- b. In general, we have anticipated that sponsors would not desire to use a reading process that necessitates reader “certification” based upon “hands on” training similar to what you have proposed for your phase 3 study. The ability to easily translate a validated reader training program into clinical practice is an important consideration. While we do not object to the reader certification process you have proposed for your phase 3 study, please be aware that we generally expect that you develop a less intense reader training process (e.g., a computerized program that describes key image interpretation characteristics, image examples and a self-contained exercise on example images) that allows accurate and reproducible image interpretation. The acceptability of this less intense reader training process would need to be assessed in a premarket study that examined (at least the following):
- sensitivity/specificity of image interpretations with respect to the histopathology standard of truth (or, for specificity, inclusion of healthy volunteers who putatively lack amyloid if insufficient autopsies are available from patients who lack amyloid). We note that including young healthy volunteers in the study sample will likely cause specificity to be biased high. If it is impossible to estimate specificity without using young healthy volunteers, an additional analysis of the young healthy subpopulation should be done so that it can be identified as such and included in the label.
  - agreement/reproducibility of image interpretations within and across readers (intra and inter-reader agreement) who examine images from
    - i. the population with histopathology standard of truth, and
    - ii. a clinically applicable patient population (e.g., patients with early signs/symptoms of dementia, mild cognitive impairment, probable Alzheimer’s disease, older healthy volunteers). Studying the clinically appropriate population will also tend to minimize the spectrum bias caused by reading the extremes of the spectrum of disease which would likely result in inflated performance estimators. We encourage evaluation of agreement for images from the older healthy adults based on their higher likelihood of a negative scan and the clinical utility of a negative scan.

Alternatives to a “less intense, computer based” reader training process may be reasonable and, if hands-on tutorials with reader “certification” are essential for accurate and reproducible image interpretations, then we wish to further discuss this necessity.

**III. You may wish to consider the concepts outlined above (item II.) as you refine your phase 3 protocol, independent reading charter, and statistical analysis plan. We express our concerns because the January 2011 advisory committee discussion**

**illustrated the potential for successful completion of a phase 3 study yet the phase 3 study provided insufficient support to allow clinical implementation of the imaging test.**

**Consequently, you may wish to address the concepts outlined above within a subsequent study that incorporates images from patients who have undergone autopsies and patients with a spectrum of cognitive impairment. In essence, this subsequent study would pool the multiple image data in a manner that uses a clinically-applicable subject-level reader training process and a clinically meaningful histopathological threshold for amyloid to assess the test sensitivity (among patients with amyloid on autopsy), specificity (among patients without amyloid at autopsy and possibly presumptively amyloid-negative volunteers) and reader agreement (intra- and inter-reader) of images across a clinically-applicable spectrum of patients (as well as within subsets of patients). To clarify, the reading queue for image interpretation would include images from subjects with and without histopathology randomized together (e.g. from GE-067-007, GE-067-005, and possibly from GE-067-015). We anticipate the need for protocol-specified success criteria for this study as well as submission of the reader training material (as feasible).**

**IV. We strongly disagree with your use of anatomic images to aid readers for the primary analysis in GE-067-007. As stated in II.a. above, premarket studies should establish the image interpretation method for clinical use. Given that you believe anatomic images will not be necessary in clinical practice, we disagree with your proposal to use anatomic images in a pivotal premarket trial. We find it unlikely that the indicated population will not include patients with brain atrophy. If you find in a pilot study that anatomic images are necessary for flumetamol PET image interpretation for subjects with atrophy, then (a) you should plan to require the acquisition and use of anatomic images for reading PET amyloid images in clinical practice and (b) the training program you plan to implement in clinical practice should include training on extracting key information from anatomic images and the method should be established in the Phase 3 trial. Use of anatomic images in the Phase 3 trial(s) will also necessitate reflection in the label.**

**V. We recommend that you consider recruiting end-of-life subjects without restriction to memory clinics in order to obtain a reasonable number of autopsy subjects who are “negative” for amyloid. We suspect that subjects recruited from memory clinics may have a higher probability of being “positive” for amyloid on histopathology. Yet autopsy subjects “negative” for amyloid are equally important to include in your primary analyses. In addition, end-of-life subjects with a short life expectancy due to non-memory causes (e.g. cancer, heart disease) may have less atrophy, which may obviate the use of anatomic images as an aid for reading PET amyloid images.**

*Question 1:*

*Does the FDA agree that, subject to the data being obtained, the proposed clinical development plan can support the following proposed indication claim?*

**FDA Response 1: No. See general comments above.**

*Question 2:*

*Does the FDA agree that our plans to provide data from the Phase 3 prospective autopsy study (GE-067-007; to estimate sensitivity) and the Phase 3 prospective study in healthy young adults (GE-067-015; to estimate apparent specificity) are acceptable to establish the validity of the visual interpretation of [18-F]flutemetamol images in detecting or excluding the presence of fibrillar A $\beta$  in the brain?*

**FDA Response 2: No. See general comments above.**

*Question 3:*

*Does the FDA agree that the autopsy study GE-067-007 is complete when the Independent Data Monitoring Committee for pathology (IDMC-P) declares that at least 22 brains that are positive for fibrillar A $\beta$  (and for which there are evaluable PET images) have been obtained and that the final number also includes other brains that have been collected prior to formal study termination?*

**FDA Response 3: No. See general comments above.**

**For subjects with histopathology, we recommend that you determine a sample size that can reliably estimate both sensitivity and specificity.**

**Justify your assumption that true sensitivity is 0.95.**

*Question 4:*

*Following a literature review showing that significant levels of fibrillar A $\beta$  are exceedingly rare in the brains of cognitively intact adults under the age of 40 years, GE Healthcare does not believe it is necessary to conduct ApoE4 genotyping of subjects in the healthy young adult study, and therefore "all comers" will be included in the primary efficacy analysis for this study. GE Healthcare welcomes the FDA's perspective on this.*

**FDA Response 4: If you determine that you must include young healthy volunteers in your primary specificity pool, we generally agree with not imposing an ApoE4 criterion for enrollment of young healthy adults who do not have a 1<sup>st</sup> degree relative with AD.**

**However, we point out that if a young healthy volunteer is amyloid "positive" on imaging and assumed to be "negative" on truth, then the specificity estimate may be lowered even though classification of this subject as a false positive may be in error.**

*Question 5:*

*Does the FDA agree with GE Healthcare's plan to supplement the blinded read of the [18-F]flutemetamol scans from the healthy young adult study with positive and negative [18-F]flutemetamol scans from a clinically relevant patient population by conducting concurrent reads of PET images from the amnesic mild cognitive impairment study GE-067-005 and the healthy young adult study, and that this approach aligns with the read process which will be used in clinical practice?*

**FDA Response 5: See FDA general comments above (particularly III.) and FDA comment 8 below.**

*Question 6:*

*Does the FDA agree with the size of the overall safety database supporting the registration of Flutemetamol F 18 Injection?*

**FDA Response 6: Yes, we generally agree.**

**Additional Comments from Division:**

**7. Histopathology:**

- a. **Justify your use of only one histopathologist for determining the CERAD score used as the standard of truth (SoT) for your primary analysis.**
- b. **Our understanding of your method to determine the CERAD score which serves as the SoT for your primary endpoint in GE-067-007 is as follows. Two samples from each of 8 brain regions will be sampled. Each sample will yield 50 sections, and silver staining will be performed on 4 of the 50 sections per sample. Since there are 2 samples per brain region, there will be 8 samples per region for which the number of neuritic plaques are counted and converted into a GE-067 Grade Score (4-point scale from 0 to 3) as in Appendix 2 of the Histology Study Plan. The GE-067 Grade Scores from these 8 samples are averaged, and if this average is  $\leq 1.5$  then a “normal” classification is assigned for the region. Clarify if our understanding is correct.**
- c. **Provide an explanation for how the subject level classification of normal or abnormal is assigned based on the region level classification of the mean GE-067 Grade Scores.**
- d. **Justify your choice of 1.5 (regional mean) as the threshold for normal versus abnormal in the modified CERAD semi-quantitation scheme. Clarify if the chosen**

**threshold corresponds to any particular number of plaque counts (e.g. 9 to 10 per field).**

- e. Clarify the degree to which immunohistochemistry (4G8 staining) is automated.**

## **8. Dose**

- a. Clarify the dose you plan to use in clinical practice if flumetamol is marketed. This anticipated dose should be the dose whose efficacy and safety are established in the Phase 3 trial(s).**
- b. We note your proposal to administer 185 to 370 MBq in GE-067-007 based on whether subjects can tolerate 30 minutes of PET imaging. We are concerned about the image quality of a 10-minute PET scan using the 370 MBq dose. We note that your single Phase 2 study and all of the other 6 Phase 3 studies use only the 185 MBq dose. Provide data to support (a) the adequacy of images obtained using 370 MBq and a 10 minute scan and (b) the higher radiation dose from the 370 MBq administration.**

## **9. Image interpretation**

- a. Justify the use of the color scale versus gray scale.**
- b. We recommend that you propose criteria for selecting image readers for your Phase 3 trials such that they would be representative of individuals anticipated to read amyloid PET images in clinical practice in the U.S. We question the frequency with which individuals without a medical degree would read amyloid PET images in clinical practice in the U.S.**

## **10. Analyses**

- a. Propose success criteria, and justification, for both sensitivity and specificity in the primary analyses.**
- b. We strongly discourage the use of majority reading when evaluating your drug. Since it is unlikely that majority reading will be the standard in clinical practice, the sensitivity and specificity estimates provided under such a study would not be representative of the performance under intended conditions of use. Please consider revising your performance study to more closely mimic clinical practice.**
- c. Uninterpretable is subjective. The number of images that are uninterpretable will change with the reader. Allowing an uninterpretable classification will likely bias high both sensitivity and specificity estimates. We understand that some equipment malfunctions or gross subject movement may absolutely cause an image to be uninterpretable.**

- i. **Pre-specify detailed criteria for un-interpretables. These criteria will be a review issue.**
  - ii. **Provide an estimated percentage of missing and/or un-interpretable images.**
  - iii. **Propose a method to avoid bias using only available data without un-interpretable images / missing values.**
  - d. **Provide detailed methods for intra- and inter-reader variability analyses.**
  - e. **Based on the review charter, readers will assign to each image set a “confidence score” from 1 to 5. Clarify the analysis plan using the “confidence score.”**
- 11. Anaphylactoid reaction: Comment on the association of Polysorbate 80 with allergic reactions based on the literature and on adverse event reports for other GE products that contain Polysorbate 80.**
- 12. The INDICATION(S) on Form 1571 (category 7) states, (b) (4)**  
[REDACTED]  
**Clarify if this is a typographical error.**

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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**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  
06/20/2011



**IND 101,866**

**MEETING MINUTES**

GE Healthcare Inc.  
Attention: Marisa Coyle  
Manager Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540

Dear Ms. Coyle:

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

We also refer to the meeting between representatives of your firm and the FDA on September 7, 2010. The purpose of the meeting was to discuss your clinical development plan supporting an original NDA Application for Flutemetamol F 18 Injection for detecting  $\beta$ -amyloid deposition.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure

MEETING MINUTES



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** EOP 2-Pre-phase 3  
**Meeting Date and Time:** September 7, 2010 2:00 pm- 3:00 pm  
**Meeting Location:** White Oak, Conference Room 1417

**Application Number:** IND 101,866  
**Product Name:** Flutemetamol F 18 Injection  
**Indication:** PET imaging for detecting brain  $\beta$ -amyloid deposition  
**Sponsor/Applicant Name:** GE HealthCare

**FDA ATTENDEES:**

Charles Ganley, M.D., Office Director, ODE IV  
Rafel Dwaine Rieves, M.D., Division Director, DMIP  
Alex Gorovets, M.D., Primary Clinical Team Leader, DMIP  
Libero Marzella, M.D., Clinical Team Leader, DMIP  
Qi Feng, M.D., Primary Clinical Reviewer, DMIP  
Jyoti Zalkikar, Ph.D., Statistical Team Leader, DMIP  
Lan Huang, Ph.D., Primary Statistical Reviewer, DMIP  
Sally Hargus, Ph.D., Pharm/Tox Reviewer, DMIP  
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader, DMIP  
Christy John, Ph.D., Clinical Pharmacology Reviewer, DMIP  
Ross Felice, M.D., Clinical Reviewer, DMIP  
Chekesha Clingman, Ph.D., Clinical Reviewer, DMIP

**SPONSOR ATTENDEES:**

Christopher Buckley, PhD, Technology Project Manager  
Yamo Deniz, MD, Global Head of Clinical Development  
Kevin Horgan, MD, Head of Internal Medicine  
Igor Grachev, MD, PhD, Clinical Project Leader  
Allison Mueller, Head of Americas, Regulatory Affairs  
Gill Farrar, PhD, Project Director  
Marisa Coyle, Manager, Regulatory Affairs

**1.0 MEETING OBJECTIVES:**

To discuss the FDA's draft comments sent to the sponsor on September 3, 2010.

**2.0 BACKGROUND:**

GE HealthCare requested an End-of-Phase 2 meeting on May 20, 2010, to discuss their Phase 3 clinical development program for Flutemetamol. Flutemetamol F 18 Injection is a positron emission tomography (PET) imaging indicated for the visual detection of brain fibrillar A $\beta$  deposition.

On September 3, 2010, FDA provided responses to the sponsor's questions submitted in their August 5, 2010 briefing package (Attachment 1). The sponsor decided to proceed with the meeting to discuss their pivotal phase 3 studies and address some of the FDA's comments.

**3.0 DISCUSSION:**

After introductions of the meeting participants, the sponsor proposed to go through their Power Point presentation (Attachment 2).

Summary of Discussion:

*The sponsor provided an overview of their normal pressure hydrocephalus (NPH) biopsy, autopsy, and new Healthy Young Adult studies.*

*As supportive evidence for the biopsy program, the sponsor discussed the virtual biopsy analysis from the phase 2 data, results from the flutemetamol (GE-067-008) biopsy study, and cited a published report from Finland showing a correlation between the biopsy and the global amyloid assessed with [ $^{11}$ C]PIB imaging.*

*FDA explained the importance of studying a diverse cohort and concerned about the homogeneity of the NPH patient group. The sponsor replied that the subjects in the NPH group were routine patients seen in the clinic as opposed to autopsy patients who were terminally ill at the time of PET scanning. The sponsor noted that 468 NPH patients in the Finland study had amyloid deposition. The sponsor stated that the pattern of amyloid seen in the flutemetamol images of NPH patients were not different from patients with Alzheimer's disease.*

*The sponsor noted that the data would be merged in an integrated visual read analysis with data from a study of young healthy volunteers using the same terminology. FDA requested the integrated results and data from the Young Healthy Adult study and asked the sponsor to clarify the retrospective and prospective biopsy data in a future submission. FDA discussed the potential risk*

*of biopsy sampling and requested the sponsor to provide reliable standard of truth estimates.*

*FDA inquired about the additional use of autopsy data to demonstrate the relevance of biopsy sampling to the global amyloid assessment. FDA stated that the numbers collected for autopsy study so far was insufficient for sensitivity or specificity. The sponsor inquired about the possibility of adding autopsy data into the integrated visual read analysis along with the data from the biopsy and healthy young adult study. FDA requested the sponsor to provide the rationale and methodology in a future submission.*

*FDA suggested that the sponsor not perform the Healthy Young Adult study at a single center and requested that scans come from different centers. FDA suggested a higher recruitment number with a sample size of 100-300 for specificity test of the investigational agent.*

*The sponsor inquired if would be acceptable to combine data from the biopsy, autopsy and Healthy Young Adult studies as the primary endpoint for developing sensitivity and specificity. FDA did not agree the pooled analyses plan since the primary endpoints in the NPH and autopsy studies are not same (see FDA response to the question 1e, below).*

*FDA expressed the importance of the labeling language for flutemetamol based on a visual read to provide the imaging physicians with information on how the PET image will be interpreted in clinical practice. The sponsor concurred.*

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# ATTACHMENT 1

## FDA Preliminary Responses

**Introductory Comment:** This material consists of our preliminary response to your questions in preparation for the meeting scheduled for **September 7, 2010** between GE Healthcare and the Division of Medical Imaging Products (DMIP). This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. 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 (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to 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. Your questions are listed below in regular font and are followed by our responses in **bold font**.

### **SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSE:**

Flutemetamol F 18 Injection is being developed to support the following indication:



1. Does FDA accept our approach to having one biopsy and one autopsy study serve as the pivotal studies in support of this indication, with additional data provided as supportive information?

#### **FDA Response:**

- A. We find your overall approach conceptually reasonable but deficient in critical details of the visual assessment methodology and the determination of performance characteristics (especially specificity) on a patient-level. We are unable, from the supplied outline, to infer a method for visual assessment of a patient's image from the regional SUVR measurements proposed by you. This is a major deficiency that must be resolved.**

**Your proposal lacks a clear description of the visual assessment process to determine the presence or absence of amyloid at a patient level. We believe such an assessment would be commonly performed by a practitioner and has to be included in your studies and eventually addressed in the labeling.**

**We do not understand how your primary endpoints, based on the SUVR of isolated cerebral regions, can lend themselves to a useful clinical interpretation of a whole-brain scan in practice. Furthermore, the two proposed biopsy studies appear to rely heavily on the assumption that the presence or absence of amyloid in a relatively circumscribed sample of brain tissue can reliably be extrapolated to a global assessment of cerebral amyloid load. Please clarify whether you make such an assumption and justify it if you do.**

**Discussion: See Discussion Summary above.**

- B. We reserve the comment on the wording of the indication statement until future discussions. However, we note that that the second component of your proposed indication is not appropriate for potential inclusion in future product labeling.**

(b) (4)

(b) (4)

**In remaining consistent with the findings of the October 23, 2008 Advisory Committee Meeting on this topic, any proposed indications for the radionuclide imaging agents for amyloid should relate solely and clearly to the potential utility of a “negative” amyloid test in ruling out a diagnosis of AD.**

**Discussion: See Discussion Summary above.**

- a. Does FDA accept the proposed designs for the above-referenced pivotal studies?

**FDA Response:**

**No, we do not accept the proposed analytical design.**

**According to the AC meeting on 10/23/2008, a “negative” amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer’s Disease (AD) and a “positive” test would have very limited utility since cerebral amyloid is known to be present in multiple conditions, including normal aging. We have previously recommended (see our comment 10.b at the telephone conference of 03-26-09) and we still recommend that you ‘bolster your plans by performing a study that ... assesses specificity within the subset of healthy young adults with presumptively no brain amyloid.’ (We can assume, without histopathology confirmation, that the healthy young adults under 40 years old are amyloid free). The inclusion of a study population widely accepted to be amyloid negative, such as younger healthy subjects, will likely provide much greater support in establishing the false positive rate of Flutemetamol imaging to be low which, as previously stated, will be critical to its ultimate clinical utility.**

**Discussion: See Discussion Summary above.**

- b. Does FDA accept our approach to use quantitative analysis of tracer uptake as the primary endpoint in the pivotal studies?

**FDA Response:**

**Please see comments above.**

**Discussion: See Discussion Summary above.**

- c. Does FDA accept the methodology employed to develop the threshold between abnormal and normal [18F]flutemetamol scans, and the proposed threshold between normal and abnormal A $\beta$  levels based on immunohistochemistry (4G8, plaque % area)?

**FDA Response:**

**Whereas we generally agree with the proposed analytical methodology for the proposed endpoints we do not understand its relationship to the assessment of Flutematol images in clinical practice.**

**Regarding the basis for the proposed threshold, we question whether a SUVR threshold generated in one relatively small trial is applicable across different trials and differently obtained data.**

- d. Does FDA accept the standard of truth (tissue A $\beta$  levels determined by immunohistochemical [primary] and histochemical [secondary] methods) in each of the pivotal studies?

**FDA Response: Yes.**

**Discussion: See Discussion Summary above.**

- e. Does FDA accept the statistical analysis plans and sample size proposed for the pivotal studies? Specifically, we plan to conduct a pooled analysis of 30 samples from two identical biopsy studies (one US IND study and one ex-US non-IND study) and an analysis of up to 26 tissue specimens/brain from at least 3 brains from an autopsy study that will be on-going during review and approval of Flutemetamol F 18 Injection.

**FDA Response:**

**A. No, we do not agree with your plan for pooled analyses. The primary endpoints in the two biopsy studies and the autopsy study are not the same. There are up to 26 SUVR values per subject in the autopsy study (GE-067-007). However, there is only one value per subject in the biopsy studies (009 and 011). The tissue location, size, type and shape are different for the two types of studies. The patient population is also different in the two types of studies (subjects with short life expectancy for 007 and Normal Pressure Hydrocephalus patients for 009 and 011). It is not appropriate to conduct the pooled analysis of all three studies. Please note that it is acceptable to pool the data for the two biopsy studies 009 and 011 because the only difference in the**

**protocols is the location. For the pooled analyses of 009 and 011, exploration should be conducted for the center effect.**

**Discussion: See Discussion Summary above.**

- B. The sample size in GE-067-007 trial is too small for assessment of sensitivity and specificity. Please justify your expectation that only three subjects (out of the planned 100 who will be imaged) will be available for efficacy analyses.**

**Discussion: See Discussion Summary above.**

2. Does FDA accept our proposal of a pooled analysis of all Phase 3 data (pivotal and supportive), as well as the methodology of analysis, to support visual interpretation of images to be included in the labeling?

**FDA Response:**

**No, we do not agree to the proposed pooled analyses given the differences in the primary endpoints and patient population, as indicated above. Please also see our earlier comments on visual assessment of images.**

**Discussion: See Discussion Summary above.**

3. Having demonstrated that [18F]flutemetamol and [11C]PiB have comparable imaging properties, does FDA agree that [11C]PiB imaging and autopsy data can be used as supportive data for the registration submission for [18F]flutemetamol ?

**FDA Response:**

**We recognize the value of C-11-PIB data as supportive but are compelled to remind you that such data do not provide independent substantiation of your drug's efficacy.**

**Discussion: See Discussion Summary above.**

4. Does the FDA agree that the overall safety database for initial registration is acceptable (at least 300 subjects)?

**FDA Response:**

**Based upon the available data, we generally agree. Please be aware that accumulating data (e.g., new safety concerns or important changes in the targeted indication) may necessitate an increase in the targeted safety database sample size.**

**Discussion: See Discussion Summary above.**

**Additional FDA Comments:**

- **For study 007, an interim analysis will occur when sixty percent of the planned subjects are available for autopsy. If there are only three subjects available for autopsy, the between variation may not be estimable in the mixed model for the primary endpoint. Please clarify the expected study duration which will assure you of obtaining enough cases for autopsy.**
- **To potentially increase the evaluable sample size in the autopsy study, you may wish to increase the time interval between PET imaging and autopsy (e.g. up to six months).**
- **Please clarify your methodology for handling missing data. What is the possible rate of missing observations?**
- **In the Study Design section of the synopsis of Study GE-067-007, you refer to the fact that a blinded visual assessment will be performed by three independent readers, however, there is no further mention of this in the description of the Statistical Methods and Planned Analysis. Please clarify.**

**4.0 DECISIONS REACHED and ACTION ITEMS:**

- **GE will submit a revised protocol when ready.**

## **ATTACHMENT 2**

Presentation Slides: End-of-Phase 2 Meeting - GE HEALTHCARE

# GE HEALTHCARE

## Flutemetamol F 18 Injection End-of-Phase 2 FDA Meeting

September 7, 2010

### Agenda

1. Summary of our understanding of FDA guidance
2. Revised clinical plan addressing guidance
3. Gain agreement on revised clinical plan

## FDA Guidance to GEHC

- appropriate indication:
  - utility of a negative scan to exclude diagnosis of Alzheimer's disease
  - NOT a positive scan to confirm diagnosis
- visual assessment (not SUVR) needs to be primary endpoint to support label
- describe visual assessment methodology
- 3 brains from autopsy study insufficient to estimate between subject variation in primary mixed model analysis
- autopsy data cannot be 'pooled' with biopsy data
- bolster plan with healthy young adult study to support specificity of the agent
- biopsy acceptable provided reliable extrapolation to a global assessment of cerebral amyloid load

<sup>3</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Biopsy can be reliably extrapolated to a global assessment of cerebral amyloid load

### Clinical

- Clinicians use frontal cortical biopsy assessment of amyloid as prognostic indicator
  - Series of 433 patients in press:
    - Leinonen et al. Annals of Neurology; in press.

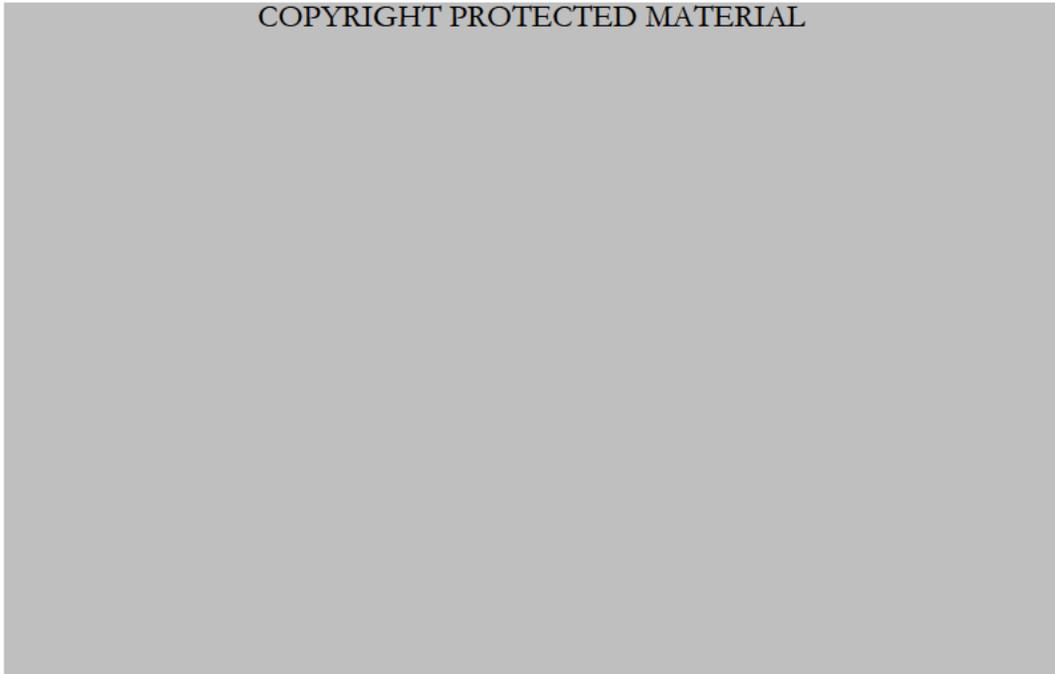
### Pathology

- Frontal lobe early site of fibrillar amyloid deposition and correlates with global cortical amyloid load
  - Naslund et al. JAMA 2000; 283:1571-1577.
  - Nelson et al. Neurosci Letters 2009; 450: 336-339.

### Imaging

- Close correlation between imaging signal from frontal cortical biopsy region and imaging signal derived from other cortical regions where amyloid is typically deposited in Alzheimer's disease
  1. **[<sup>11</sup>C]PiB imaging Biopsy Study:**
    - Leinonen et al. Arch Neurol. (2008) 65(10):1304-9.
  2. **Flutemetamol imaging: "Virtual biopsy" analysis of study ALZ201**
  3. **Flutemetamol imaging: Biopsy study GE-067-008**

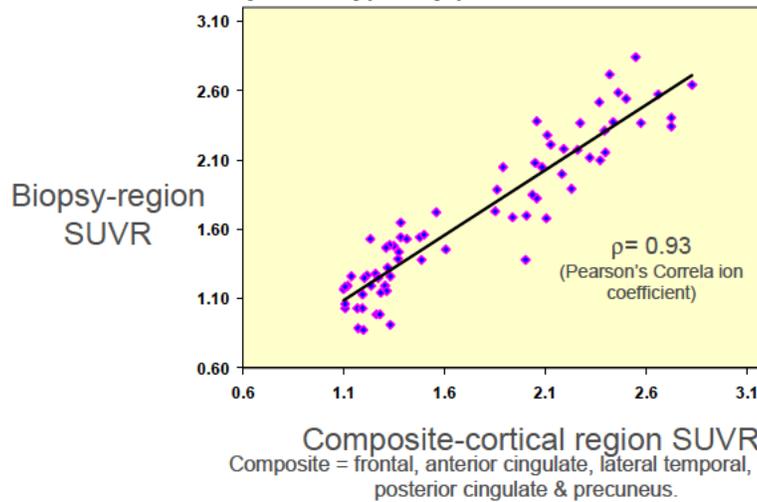
<sup>4</sup>  
Meeting with FDA  
7<sup>th</sup> September



\* Reproduced from Leinonen et.al. [ARCH NEUROL/VOL 65 (NO. 10) 2008] & Annotated with correlation.

## GE Study ALZ201 (n=72)

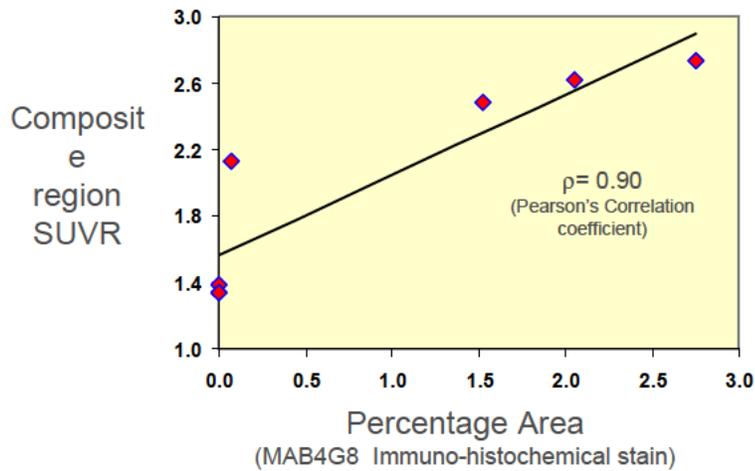
Frontal **virtual** BIOPSY region [<sup>18</sup>F]flutemetamol signal is representative of signal from composite cortical regions of the brain where amyloid is typically present in Alzheimer's disease



6  
Meeting with FDA  
7<sup>th</sup> September

## Study GE-067-008 (n=7)

Comparison of tissue based amyloid measurement with [<sup>18</sup>F]flutemetamol *in vivo* PET-based measure



### Biopsy can be reliably extrapolated to a global assessment of cerebral amyloid load

1. Frontal Biopsy Pathology vs Frontal SUVR (Leinonen et al)
2. Frontal SUVR vs Global SUVR (ALZ201)
3. Frontal Biopsy Pathology vs Global SUVR (GE-067-008)
4. Frontal Biopsy Pathology vs Global Pathology: To be addressed (GE-067-007)

## Risk/Benefit of Biopsy Compared to Autopsy

### Biopsy

- Benefits:
  - clinically relevant patient population
  - *in vivo* tissue acquisition with immediate preservation
  - interval between scan and tissue acquisition a few days
- Risks:
  - Low probability of false positive scans: missed amyloid – prejudice against our analysis

### Autopsy

- Benefits:
  - global assessment
- Risks:
  - Terminally ill patient data dubious relevance to clinical practice
  - Results may be compromised due to post-mortem artifacts

<sup>9</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Revised Proposal for Registration (I)

### Integrated analysis to support registration

- Biopsy Studies
  - 009/011
  - 010
- Healthy young adult study

### Primary endpoint for integrated analysis now visual inspection

<sup>10</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Revised Proposal for Registration (II)

**New Study:** Healthy young adults (<40yrs)  
scanned with [<sup>18</sup>F]flutemetamol (n=30)

Primary Endpoint: visual read

FDA: Assume without histology confirmation  
healthy young adults (ApoE4 negative)  
under 40 years old are amyloid free

<sup>11</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Revised Proposal for Registration (III)

### Primary Visual Inspection Analysis

Sensitivity and Specificity of visual read  
performance will be based upon the pooled  
results (n=70) from

- Biopsy study (009/011) (n=30)
- Healthy Young Adult Study (n=30)
- Retrospective biopsy study (010) (n =10)

<sup>12</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Autopsy Study

First objective (primary endpoint): define concordance between PET signal and amyloid pathology, regionally and globally

- Increase n from 3 brains to 6 brains to enable reliable estimate of between subject variation in a mixed model analysis
  - Up to 26 comparisons brain yielding up to 150 paired data points
  - Supporting hypothesis that flutemetamol signal is consistently proportional to amyloid load

Second objective (new): define relationship between biopsy area and other regions of the brain relevant to diagnosis of Alzheimer's disease

- **Pathology:** quantify numeric relationship of frontal cortical biopsy amyloid to regional and global amyloid load
- **Imaging:** quantify numeric relationship of frontal cortical biopsy SUVR to regional and global SUVR
  - Confirming that biopsy provides data that is representative of regional and global assessments

13  
Meeting with FDA  
7<sup>th</sup> September

## Incorporating FDA Guidance

- biopsy acceptable: reliable extrapolation to global assessment of cerebral amyloid load
- biopsy visual assessment now primary endpoint to support label
- plan bolstered with healthy young adult study to support specificity of the agent
- autopsy data will not be pooled with biopsy data
- biopsy data and healthy young adult data will be pooled
- sample size of autopsy study increased to 6 brains to provide supportive data for use of biopsy
- visual assessment methodology described

14  
Meeting with FDA  
7<sup>th</sup> September

## Revised Proposal for Registration (II)

**New Study:** Healthy young adults (<40yrs)  
scanned with [<sup>18</sup>F]flutemetamol (n=30)

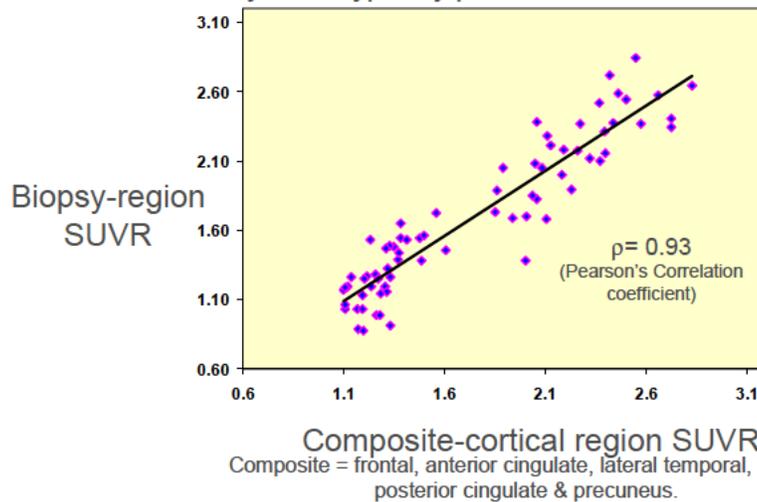
Primary Endpoint: visual read

FDA: Assume without histology confirmation  
healthy young adults (ApoE4 negative)  
under 40 years old are amyloid free

11  
Meeting with FDA  
7<sup>th</sup> September

### GE Study ALZ201 (n=72)

Frontal **virtual** BIOPSY region [<sup>18</sup>F]flutemetamol signal is representative of signal from composite cortical regions of the brain where amyloid is typically present in Alzheimer's disease



8  
Meeting with FDA  
7<sup>th</sup> September

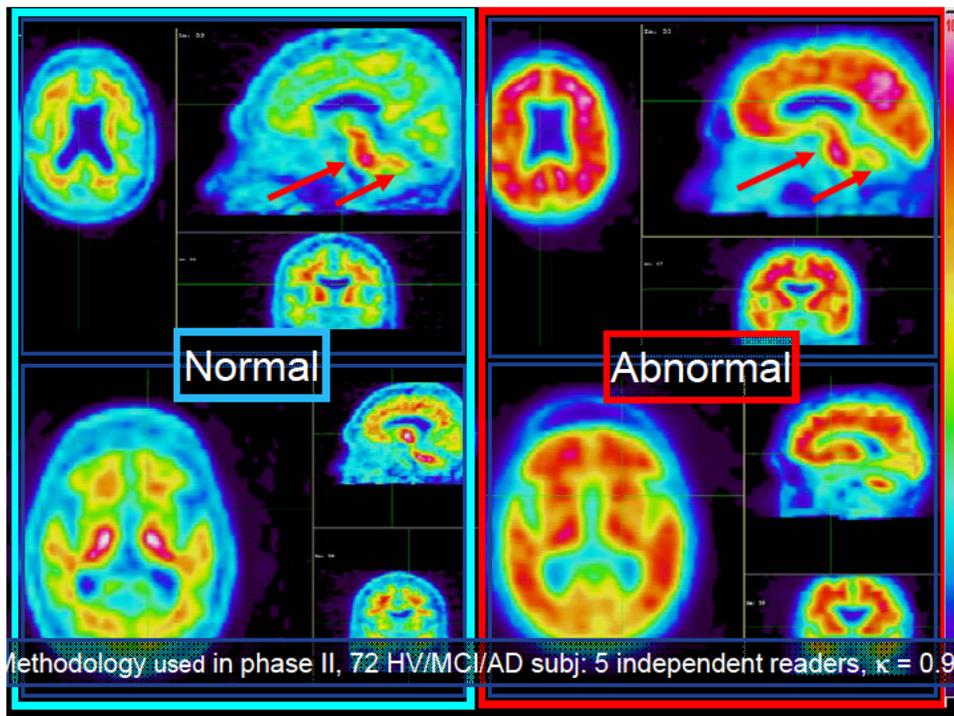
### Basic Image Review Methodology for visual detection of A $\beta$

1. Navigation to longitudinal fissure for **sagittal** review
2. MPR crosshair mid ventricle
  - ❖ Reference **REGION** visible – cerebellum (blue/green)
  - ❖ Assess frontal/anterior cingulate, posterior cingulate/precuneus & occipital
  - ❖ Cortical tracer uptake compared to cerebellum
    - ❖ blue/green = **NORMAL**
    - ❖ Yellow/red/pink = **ABNORMAL**
3. Repeat in other hemisphere
4. Continue with a superior to inferior axial review
  - ❖ Assess frontal, parietal, precuneus, cinguli, lateral temporal, occipital, inferior frontal & striatum
5. An abnormal finding in any of these regions provides a result of **ABNORMAL**

Abnormal

Ref/normal

*Methodology based on phase I data, ratified in phase II*



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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  
10/06/2010



IND 101866

MEETING MINUTES

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

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

We also refer to the meeting between representatives of your firm and the FDA on April 12, 2012. The purpose of the pre-NDA meeting was to discuss the content and format of the NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** April 12, 2012, 3:00 PM  
**Meeting Location:** White Oak, Bldg. 22, Conference Room 1421

**Application Number:** 101866  
**Product Name:** Flutemetamol F18 Injection  
**Indication:** PET imaging for detecting brain amyloid deposition.  
**Sponsor/Applicant Name:** GE Healthcare (GEHC)

**FDA ATTENDEES:**

Rafel Rieves, MD, Director, Division of Medical Imaging Products (DMIP) / *Meeting Chair*  
Liberio Marzella, MD, Deputy, Division Director, DMIP  
Alex Gorovets, MD, Clinical Team Leader, DMIP  
Lucie Yang, MD, PhD, Primary Medical Team Leader, DMIP  
Phillip Davis, MD, Primary Reviewer, DMIP  
Scheldon Kress, MD, Medical Officer, DMIP  
Ravindra Kasliwal, PhD, Clinical Reviewer, ONDQA  
Robert Mello, PhD, Microbiologist, OPS/NDMS  
Jyoti Zalkikar, PhD, Statistical Team Leader, DMIP  
Anthony Mucci, PhD, Statistical Reviewer, DMIP  
Sally Hargus, PhD, Pharm/Tox Reviewer, DMIP  
Gene Williams, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCP5  
Christy John, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCP5  
Sharon Thomas, Regulatory Project Manager, DMIP / *Meeting Recorder*

**SPONSOR ATTENDEES:**

Fred Longenecker, Director, Regulatory Affairs  
Paula Clark, Senior Manager, Regulatory Affairs  
Gillian Farrar, PhD, Senior Program Director  
Christopher Buckley, PhD, Imaging Technology Leader  
Paul Sherwin, MD, PhD, Senior Medical Director  
Yamo Deniz, MD, Global Head of Clinical Development & CMO  
Paul Jones, PhD, Senior Scientist, R&D  
Daniel Frenia, QA Director-HC  
Roald Skurtveit, PhD, PCS Project Leader  
Bimal Patel, Regulatory Affairs, CMC Advisor  
Shamsul Alam, PhD, Biostatistics Leader, R&D

(b) (4)

**1.0 MEETING OBJECTIVES:**

To discuss the FDA's preliminary comments sent to the sponsor on April 10, 2012.

**2.0 BACKGROUND:**

On February 6, 2012, the sponsor submitted a type B, pre-NDA meeting request to discuss the content and format of a new drug application (NDA) for flutemetamol. The sponsor anticipates submitting the NDA in October 2012.

On April 10, 2012, FDA provided preliminary responses to the sponsor's questions submitted in the March 9, 2012 meeting package. On April 11, 2012, the sponsor decided to proceed with meeting to obtain clarification on questions 2, 3, 4, 7, 8 and item 15 under Other FDA Comments. The sponsor also provided a "Summary of Understanding" (Attachment 1) to support the discussion. The questions submitted by the sponsor are presented below in italics, followed by FDA's preliminary responses in bold text. The discussion points are shown in *bold italics* below.

**3.0 DISCUSSION:**

After introductions of the meeting participants, the sponsor proposed to go through their "Summary of the Understanding" document (Attachment 1).

**3.1 CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)**

*Sponsor's Question #1:*

*Does the FDA agree that the structure and format of information provided in Module 3 is acceptable for filing?*

**FDA's Preliminary Response #1:**

**The proposed formatting of the CMC section appears to be reasonable. The acceptability of the information in each of the NDA section will be evaluated at the time of NDA review.**

**Discussion point #1:**

***This question was not discussed.***

*Sponsor's Question #2:*

*Does the FDA have any comments with the general manufacturing and process controls used to manufacture Flutemetamol F 18 Injection?*

**FDA's Preliminary Response #2:**

- a. We would consider (b) (4) and compound (b) (4) along with (b) (4) to be the starting materials for the manufacture of Flutemetamol F 18 drug. Compound AH111907 is considered to be the final intermediate. The final intermediate is considered to be manufactured and

- sent to the PET drug product manufacturer as an (b) (4) material. Appropriate controls should be provided for each in the NDA.
- b. In the elucidation of structure and other characteristics (3.2.S.3.1), data to support that the radioactive Flutemetamol F 18 is the same as Flutemetamol reference standard lot should also be provided.
  - c. Clarification should be provided whether unit dose or multidose vials (or syringes) are intended to be marketed under the NDA.
  - d. In the drug product specifications (test, test procedure, and acceptance criteria) for specific activity, membrane filter integrity, ethanol, polysorbate 80 and any residual solvents should be included.
  - e. Clarify the term “flutemetamol and related impurities” indicated in the chemical purity test.
  - f. The final intermediate appears to contain structural features (b) (4) (b) (4) that generally can render a material to be mutagenic. We would expect that the drug product manufacturing and purification process would be capable of removing the precursor (and other related materials) from the final purified drug product. You may need specification with adequate acceptance criterion for residual amount of precursor in the final drug product.

**Discussion point #2:**

- a. FDA noted that the information submitted in the pre-NDA briefing package for GMP starting materials appear to be not for the starting materials as identified in FDA response 2a above. The sponsor confirmed that the GMP starting materials were indeed as identified in 2a above and that they would submit appropriate controls for them in the NDA.
- b. FDA requested for identifying (confirmation of structure) the radioactive compound correlation with established non radioactive reference standard should be performed using two orthogonal methods.
- c. The sponsor confirmed that 10 ml and 30 ml multi dose vials will be marketed under the NDA.
- d. FDA noted the submission lacked certain tests in the drug product specifications. The sponsor explained why the tests were unnecessary. FDA asked the sponsor to provide justification in the justification section in the NDA. The sponsor asked if additional tests were necessary, if the product needs to (b) (4) integrity testing. FDA confirmed that if the (b) (4) integrity was checked, verified and uncompromised additional tests were unnecessary. The sponsor asked for clarification on the inclusion of ethanol and residual solvents. FDA recommended testing for ethanol since it is a (b) (4) excipient and bears a quantitative statement on the label.

*FDA indicated that residual solvents, (b)(4) which are class 2 and class 1 solvents, respectively, should be part of the release testing. Skip lot testing for solvents is not acceptable. The sponsor inquired that it will be possible to not perform solvent testing if they can show that they are able to achieve control over the solvent content by other process controls. FDA indicated that if adequate correlation for the rationale supported by data, and process controls are provided in the NDA, then FDA would consider such a proposal. FDA also indicated that in such case, the residual solvent specification will still be part of specification (acceptance criteria and regulatory test procedure should be in the NDA), but such process control model can be alternate method where when the indicated process control is met it would ensure that the residual solvent is within the limits.*

*FDA also recommended pH as part of the release testing. FDA also indicated that osmolality data for the validation batches should be provided.*

- e. *The sponsor clarified the term “flutemetamol and related impurities” as indicated in the chemical purity test portion of the meeting package. The sponsor explained that the Final Intermediate and any other impurities with similar structural features that were present in the drug product are captured in the specification parameter for flutemetamol and related impurities. FDA recommended that specification limit of (b)(4) should be reduced and referred the sponsor to the draft guidance for genotoxic impurities. FDA asked if the hydrolysis product of the precursor is a structure for genotox materials. FDA further indicated that in the labeling, there would need to be statement regarding the flutemetamol mass amount (range is acceptable) and asked the sponsor that there should be test (release test) to support such statement.*

*FDA stated that the potentially genotoxic impurity in the Final Product may not have been adequately qualified for safety, because the test articles used in GLP studies appeared not to have contained the potentially-genotoxic-impurity. FDA requested that the sponsor provide a table of the individual test articles used in each pivotal nonclinical GLP study, and the impurity profile for each test article. The sponsor stated that the test articles used in GLP studies were essentially 100% Flutemetamol containing no impurities, and that the impurities present in the Final to-be-marketed Product are present due to the radiochemical synthetic process. The sponsor stated that it would provide a report in which the risks of genotoxicity in the Final Product were addressed and justified. FDA stated that the acceptability of the justification would be a review issue.*

Sponsor's Question #3:

*Does the FDA agree that any additional manufacturing sites added post-approval would not be required to present stability data in an NDA supplement, but rather conduct routine stability studies as part of their annual commitment?*

**FDA's Preliminary Response #3:**

**a. CMC:**

**If the PET drug product formulation, method of manufacture (including that of final intermediate (precursor), manufacturing scale, strength and controls remain the same, then additional stability studies may not be necessary in the NDA supplement. However, you will still need to submit data from three batches from the new site in support, with other necessary information.**

**b. Microbiology:**

**Additional manufacturing sites added post-approval would need to be qualified and the NDA supplement should contain summary batch analysis data (covering sterility, bacterial endotoxins, sterilizing (b) (4) integrity) from each site. In addition, summary results of aseptic processing validations will need to be submitted for each new site.**

**Discussion point #3:**

***The sponsor confirmed that they would submit three validation batches from each new site added in support of each sNDA. The sponsor agreed with the microbiology requirement for the addition of each new site added post-approval.***

**NON CLINICAL**

**Sponsor's Question #4:**

***Does the FDA find the non-clinical package adequate to support the Flutemetamol F 18 Injection NDA application?***

**FDA's Preliminary Response #4:**

**Yes.**

**a. Reviewer's comment on proposed Package Insert (PI):**

**The following statement in 13.2 Animal Toxicology and /or Pharmacology is not supported by the data:**

**[REDACTED]** (b) (4)

**In study B067056, there were mortalities, although not attributed to Flutemetamol. Please revise the statement in the PI.**

- b. Additional nonclinical request: Your summaries of nonclinical studies (Table 1 and Table 2) indicated several nonclinical studies were conducted, but have not been submitted. Please submit all listed nonclinical final study reports to the IND.**

**Discussion point #4:**

- a. GEHC agreed with the recommendation to revise the PI to include the statement in section 13.2 that deaths were not attributed to Flutemetamol in study B067056. FDA did not object to the sponsor's proposed verbiage.**
- b. GEHC stated that they would submit all listed nonclinical final study reports to the IND.**

**CLINICAL**

**Sponsor's Question #5:**

*Studies GE-067-007, 015 and 020 are the principal phase 3 studies to support US registration of Flutemetamol F 18 Injection for the proposed indication. For on-going Phase 3 Study GE-067-005, only the results of the reader agreement will be provided in the NDA. The remaining studies [Phase 3 biopsy studies GE-067-008, 009, 010 and 011; Phase 2 ALZ201; and, Phase 1 studies ALZ103 and GE-067-014] are to be deemed supportive for registration, along with a literature summary. Does the FDA agree with this approach to support registration?*

**FDA's Preliminary Response #5:**

**We agree this is a reasonable approach for your NDA submission.**

**Discussion point #5:**

***This question was not discussed.***

**Sponsor's Question #6:**

*The overall safety database for Flutemetamol F 18 Injection includes a total of 761 subjects, including approximately 581 subjects who received a dose of 185 MBq, and approximately 180 patients who received a dose of 370 MBq. Does the FDA agree that the overall safety database for Flutemetamol F 18 Injection is adequate for filing?*

**FDA's Preliminary Response #6:**

**The number of stated patients in your database seems adequate. Please note you will need to include all patients administered Flutemetamol F18 Injection (at any dose level) in the safety data submitted with your NDA submission.**

**Discussion point #6:**

***This question was not discussed.***

Sponsor's Question #7:

*In compliance with the Pediatric Research Equity Act of 2003, on June 6, 2011, (Serial No. 0034) GE Healthcare submitted a request for a full waiver of pediatric studies, as Flutemetamol F 18 Injection does not address a medical need in pediatric patients but rather is to be indicated in adult patients who present with signs and symptoms of a cognitive disorder.*

**FDA's Preliminary Response #7:**

**We agree that a request for full waiver of pediatric studies for Flutemetamol F18 Injection is reasonable. This request will be addressed after we receive your NDA submission.**

Discussion point #7:

*The sponsor stated that they would request for full waiver of pediatric studies in the NDA submission.*

**LABELING**

Sponsor's Question #8:

*Does the FDA have any comments on the draft labeling proposals outlined in the attached draft labeling?*

**FDA's Preliminary Response #8:**

**We recommend incorporating important aspects regarding image interpretation methods into section 2.6 of the label. This should include what distinguishes a positive from a negative Flutemetamol F18 scan. Additionally, we refer you to the Non-Clinical team's response (a) to question # 4.**

Discussion point #8:

*The sponsor asked if they had an option to display the scans in the package insert in either color or black-and-white. FDA asked if the majority of readers used color images in the training program. The sponsor stated that the images were displayed by default in the color scale and the readers were able to switch to further evaluate the images. FDA asked the sponsor to provide data to distinguish when the readers switched and read from color to black-and-white. FDA explained that the sponsor had not standardized the image display sufficiently if some, but not all, readers used color images in the confirmatory studies. FDA noted that the sponsor will need data to show that it does not make a difference. The sponsor agreed to implement the information in their definitive study (study 21) in a manner that ensured standardization in image display.*

**ADMINISTRATIVE**

Sponsor's Question #9:

*Does the FDA envision an advisory committee for this NDA?*

**FDA's Preliminary Response #9:**  
**It is premature to comment at this time.**

**Discussion point #9:**  
***This question was not discussed.***

**Sponsor's Question #10:**  
*Does the FDA envision any post-approval commitments for this NDA?*

**FDA's Preliminary Response #10:**  
**It is premature to comment at this time.**

**Discussion point #10:**  
***This question was not discussed.***

## **OTHER FDA COMMENTS**

### **11. NDA/sNDA Presentations to CDER's Division of Medical Imaging Products**

The Center for Drug Evaluation and Research's Division of Medical Imaging Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation IV should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

**Discussion point #11:**  
***This comment was not discussed.***

### **12. FINANCIAL DISCLOSURE FINAL RULE**

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 “*Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure By Clinical Investigators*” at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm>.

**Discussion point #12:**  
*This comment was not discussed.*

**13. PEDIATRIC RESEARCH EQUITY ACT (PREA)**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

**Discussion point #13:**  
*This comment was not discussed.*

**14. DEMOGRAPHICS**

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data “by gender, age, and racial subgroups” in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG
Gender	Males	All Females	Females >50
Age:	0-#1 Mo.	>1 Mo.-#2Year	>2-#12
	12-16	17-64	65
Race:	White	Black	Asian
	Other		

**Discussion point #14:**

*This comment was not discussed.*

**15. QT EVALUATION**

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Alternative proposals to the "TQT" study may be appropriate.

**Discussion point #15:**

*The sponsor asked if the above hERG-1 study was sufficient to assess QT-prolongation. FDA explained that in vitro data is insufficient; submission of human in vivo evaluation of QT is standard for NDA submissions. FDA then explained that the sufficiency of the data acquired in 743 patients is a power issue, and that the NDA submission should include an estimation of the power of the data to show QT-prolongation. Specifically, using a confidence interval approach, what QT change can be ruled out from the data? The sponsor agreed to provide this information in the NDA.*

**16. OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (OSE)**

- If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

**Discussion point #16:**

*This comment was not discussed.*

**4.0 ISSUES REQUIRING FURTHER DISCUSSION:**

- FDA to comment on the Reader Training Program, Supplemental Question (Attachment 1) / GEHC's e-mail dated April 10, 2012.

**5.0 ACTION ITEMS:**

1. GEHC to submit all listed nonclinical final study reports to the IND.
2. GEHC to submit the training validation protocol GE-067.

**6.0 ATTACHMENTS:**

- Attachment 1 - GE Healthcare Summary of Understanding

**7.0 POST-MEETING ADDENDUM: READER TRAINING PROGRAM**  
(FDA's e-mail correspondence submitted on April 25, 2012.)

- Based on your brief proposal on nuclear medicine technologists in the training validation protocol GE-067 that was summarized in your 10 April 2012 email we have no objections to your plan. If there are additional details you intend to incorporate into your full protocol for GE-067, we reserve comment on the full protocol until it is submitted.

# ATTACHMENT 1

## Flutemetamol F 18 Injection April 12, 2012 Pre-NDA Meeting GE Healthcare Summary of Understanding

If the Final Intermediate or any other impurities with similar structural features were present in the drug product, then this would be captured in the specification parameter for flutemetamol and related impurities. This specification has a limit of not exceeding (b) (4)

### FDA's Response 3:

- a. We would like to thank FDA for its response that additional stability may not be necessary in the sNDA for the addition of manufacturing sites added post-marketing. Further, we will submit three validation batches from each new site added in support of each sNDA.
- b. Microbiology: Thank you for your response. GEHC agrees with the microbiology requirement for the addition of each new site added post-approval.

### NON CLINICAL

#### FDA Response 4:

- a. We thank the FDA for their comment. Because the mortalities observed in study B067056 were not attributable to flutemetamol, we propose to revise labeling Section 13.2 Animal and Toxicology and/or Pharmacology, with the following verbiage:

(b) (4)

- b. Thank you for your comment. All non clinical studies that have not been submitted to the IND to date will be submitted to the IND prior to submission of the NDA.

### CLINICAL

#### FDA Response 5:

We would like to thank the FDA for their response. We have no further comment.

**FDA Response 6:**

We would like to thank the FDA for their response. We have no further comment.

**FDA Response 7:**

We thank FDA for its response that a full waiver of pediatric studies for Flutemetamol F 18 Injection is considered reasonable and will be addressed in our NDA submission.

**LABELING**

1. We thank FDA for its response. We will be including important aspects of image interpretation methods in Section 2.6 of the label, including what distinguishes a positive from a negative [<sup>18</sup>F]flutemetamol scan. We view the information provided in the package insert as supplemental to the reader training program which you asked us to prepare and validate. In light of this, it was our plan to provide black and white images in our package insert instead of color images. It is our belief that the image interpretation should be emphasized in the reader training program and that the package insert would serve as a reminder of the key points of evaluating a flutemetamol image rather than a detailed guide to image interpretation. *Does FDA find this approach acceptable?*

2. While preparing for this meeting we noted the recent FDA approval of florbetapir and its approved package insert. It is our belief that this document provides an indication of the Division's expectations for the format and basic content of labeling for this class of compounds, including flutemetamol. *Is our understanding correct?*

**ADMINISTRATIVE**

**FDA Response 9:**

Thank you. We appreciate that the decision of an Advisory Committee Meeting cannot be determined at this time.

**FDA Response 10:**

We thank the FDA response to this question.

**OTHER FDA COMMENTS:**

11. We will contact the project manager shortly after the NDA/sNDA submission to schedule a date for our presentation.

12. Financial disclosure will be provided in the NDA.

13. We thank FDA for providing a full waiver for pediatric studies for Flutemetamol F 18 Injection.

14. Safety and effectiveness will be provided by gender, age, and racial groups in the NDA.

15. A nonclinical study was conducted (“Effects on hERG Tail Current”) to assess the potential of flutemetamol to induce QT-prolongation. This in vitro test investigated the potential for inhibition of the rapid delayed rectifier potassium current (hERG-1). Flutemetamol was negative in this test. In vivo in dogs, flutemetamol did not induce any effects when administered at the maximum dose in both a single administration cardiovascular study and in the 14-day repeat dose study.

We have QTc data in 743 subjects in the clinical program. There was no indication of clinically relevant QTc prolongation. There were no adverse events consistent with QTc prolongation, and no reported cases of Torsades de Pointes. *Given these results, does FDA agree that this is sufficient?*

16.

- There is no information on product medication errors to report.
- The proprietary name, VIZAMYL was submitted to FDA and conditionally accepted by the Agency on November 29, 2011.

## SUPPLEMENTAL QUESTION

As follow-up to our March 6, 2012 teleconference with the Agency to discuss our reader training program for flutemetamol PET images, the GEHC team has been working to incorporate FDA expectations and guidance for both the training program and the validation protocol, especially in regard to the addition of a separate training module for nuclear medicine technologists (NMTs) on proper orientation of flutemetamol PET images. In doing so we are paying close attention to Agency guidance that as much as possible we mimic clinical practice and that the NMTs who take part in the validation protocol not be from a central facility, but are involved in routine nuclear medicine clinical practice. We want to ensure that our interpretation of the Agency guidance is correct and would appreciate if the clinical reviewers (specifically Drs. Davis and Yang) would be willing to let us know if they find our proposed interpretation (summarized below) acceptable. We realize that this is not a formal request but are hopeful that we could take five minutes at the end of the April 12 pre-NDA meeting to gain feedback from FDA to make sure we are in agreement.

### GEHC Proposal for NMTs in training validation protocol GE-067

The NMTs will complete the orientation module of the disk training program.

The 300 flutemetamol PET images for the validation study will be randomized and divided into 5 equal sets of 60 images. Each of the five NMTs will be responsible for orienting one-fifth (60) of the images. The five sets of oriented images will then be combined and re-randomized into five new sets of oriented images for the blinded image evaluations.

Each of five blinded nuclear medicine physician readers will be randomized to read one of the five full sets of 300 randomized, oriented images. This process will ensure that each reader will receive images oriented by each of the five NMTs, which will mimic clinical practice where there often are multiple NMTs supporting the readers at a clinical site. We believe this design is more effective and a better representation of clinical practice than assigning NMT and reader pairs, and that it will serve as internal validation of the ability of the individual NMTs to orient images properly.

Each nuclear medicine physician reader will also have taken the orientation training module and during their read sessions will be asked to assess whether each image is properly oriented. If they do not believe that an image is properly oriented they will send that image back for reorientation by an NMT, until the reader considers the image to be properly oriented for reading.

Because the NMTs will have to take personal time off from their regular NMT clinic responsibilities in order to participate in this protocol we felt that asking them to be on call for possible reorientation was more than we could expect of them personally and professionally. Therefore, we propose having a different set of NMTs on-call (one for each day of the blinded reads) during the blinded reads. These NMTs will have to meet the same inclusion / exclusion criteria and have to take and pass the same orientation training module as will the NMTs who will perform the original image orientations. All NMTs will be actively employed in a nuclear medicine clinic. We believe that this use of a different group of NMTs will help mimic clinical practice in which a different NMT may be on duty and thus called upon to reorient an image that a reader considers needs additional work.

Does the agency consider this proposal acceptable? If not, what guidance would you give to us?

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/s/  
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SHARON P THOMAS  
05/09/2012



**IND 101866**

**MEETING MINUTES**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Flutemetamol F18 injection.

We also refer to the telecon between representatives of your firm and the FDA on October 25, 2011. The purpose of the meeting was to discuss your updated clinical development plan for Flutemetamol.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type C/ Teleconference

**Meeting Date and Time:** October 25, 2011, 1:00 PM to 2:30 PM

**Meeting Location:** White Oak, Bldg. 22, Conference Room 2201

**Application Number:** 101866

**Product Name:** Flutemetamol F18 Injection

**Indication:** PET imaging for detecting brain amyloid deposition.

**Sponsor/Applicant Name:** GE Healthcare (GEHC)

### FDA ATTENDEES:

Rafel Dwaine Rieves, M.D., Division Director, DMIP (*Meeting Chair*)  
Liberio Marzella, M.D., Deputy, Division Director, DMIP  
Alex Gorovets, M.D., Clinical Team Leader, DMIP  
Lucie Yang, M.D., Ph.D, Primary Medical Team Leader, DMIP  
Qi Feng, M.D., Ph.D. Primary Clinical Reviewer, DMIP  
Jyoti Zalkikar, Ph.D., Statistical Team Leader, DMIP  
Anthony Mucci, Ph.D., Statistical Reviewer, DMIP  
Lan Huang, Ph.D., Primary Statistical Reviewer, DMIP  
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DMIP  
Sharon Thomas, RPM, Sr. Regulatory Project Manager, DMIP (*Meeting Recorder*)

### SPONSOR ATTENDEES:

Shamsul Alam, PhD, Biostatistics Leader  
Karen Briegs, Senior Program Director, PET Segment Leader  
Christopher Buckley, PhD, Technology Project Manager  
Paula Clark, Senior Manager, Regulatory Affairs  
Yamo Deniz, MD, Global Head of Clinical Development  
Gill Farrar, PhD, Senior Program Director  
Allison Mueller, Head of Americas, Regulatory Affairs  
Francois Nicolas, Director of Neurology, PET Segment  
Paul Sherwin, MD, PhD, Senior Medical Director  
Adrian Smith, PhD, Histopathologist

### EXTERNAL CONSULTANT TO GEHC:

(b) (4)

### **1.0 MEETING OBJECTIVES:**

To discuss the FDA's draft comments sent to the sponsor on October 21, 2011.

### **2.0 BACKGROUND:**

On August 5, 2011, the sponsor requested a Type C, Guidance meeting to discuss their updated clinical development plan. This meeting request was submitted in response to the FDA's Advice/Information Request Letter dated June 20, 2011. On October 21, 2011, FDA provided preliminary responses to the sponsor's questions submitted in their September 21, 2011 briefing package (Attachment 1). On October 23, 2011, the sponsor decided to proceed with the teleconference and submitted a "Summary of the Discussion" on October 25, 2011.

### **3.0 DISCUSSION:**

After introductions of the meeting participants, the sponsor proposed to go through their Summary document (Attachment 2).

#### Summary of Discussion:

*The sponsor provided an overview of studies GE-067-007, GE-067-009, -010, -011, and GE-067-015 (Studies 007, 009, 010, 011, 015). The sponsor asked FDA to comment on whether study GE-067-020 (Study 020) was pivotal for deriving both sensitivity and specificity, as well as for the determination of reader agreement as measured by kappa. FDA responded that great emphasis will be placed on Study 020 for efficacy verification and clinical implementation. FDA stated that Study 020 evaluates the reader training method and agreement among the readers. Thus, the results of Study 020 will likely be reflected in the labeling.*

*The sponsor explained that GE-067-005 (Study 005) is an ongoing phase 3 study intended to support label expansion post-approval. Images from Study 005, a phase 2 study (GE-067-201), and two phase 1 studies (GE-067-103, GE-067-014) will be added to images from Studies 007, 009, 010, 011, and 015 for assessment of reader agreement in Study 020. FDA agreed with the sponsor's proposal.*

*The sponsor stated that there would be 5 readers for Study 020, and the readers would not have experience reading amyloid images. The primary endpoint would be met if the lower bound of the 95% confidence interval for sensitivity and specificity is >70% for at least 3 (the same 3) of the 5 readers. The sponsor agreed to submit a statistical analytical plan (SAP). Kappa scores for subject subsets (MCI, end of life, etc) as well as for all readers together, and pairwise, would be reported for Study 020.*

*The sponsor discussed the number of subjects and the analyses of reader agreement in their phase 2/3 studies.*

*The sponsor noted that a Contract Research Organization (CRO) will conduct Study 020 to include blinded read evaluations and they will recruit readers independent of the firm. The sponsor stated that the readers will use the CD to train. FDA inquired about the work stations in rural areas compared to a metropolitan PET imaging department. The sponsor stated that standard workstations would be used and agreed to describe the workstation in the Image Review Charter.*

*The Sponsor explained that Study 005 and Study 015 injected 185 MBq and images were read with a 10 minute scan time. In Study 007 either 370 MBq was injected and images were read with a 10 minute scan time or 185 MBq was injected and images were read with a 20 minute scan time. The sponsor explained that imaging was performed for 30 minutes, and there was imaging signal equivalency between the two dose / reading scan time paradigms used in Study 007. FDA did not object to the sponsor's proposed dose of 185 MBq with a 20-minute acquisition time for the label though it is premature to discuss labeling prior to reviewing the data.*

*FDA inquired about the uninterpretable images. The sponsor proposed that uninterpretable images will not be a forced diagnosis but would be considered unevaluable. The sponsor agreed to address uninterpretable scans within the Study 020 protocol, Statistical Analysis Plan, and Case Report Form.*

*For the biopsy studies 008, 009, 010 and 011, FDA inquired about how tissue samples were obtained. The sponsor explained that one brain biopsy sample from the frontal or parietal cortex was taken per subject, according to local clinical practice.*

*FDA requested protocol GE-067-020 prior to its implementation, along with the web-based training CD. FDA agreed to review and provide feedback on the CD in a timely manner.*

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

There were no unresolved issues.

**5.0 ACTION ITEMS:**

1. GEHC to submit CRFs, Image Review Charter, SAP an updated protocol for GE-067-020.
2. GEHC to provide the web-based training CD.

**6.0 ATTACHMENTS:**

- Attachment 1 - FDA Preliminary Responses
- Attachment 2 - GEHC Summary of Understanding

# ATTACHMENT 1

## FDA Preliminary Responses

### Sponsor Questions and Division Response (Qs in *italic* and draft As in **bold**)

#### FDA Preliminary Responses IND 101866 Flumetamol Injection

This material consists of our preliminary response to your questions and additional comments in preparation for the discussion at the Type C teleconference scheduled for **October 25, 2011** between **GE Healthcare** and FDA. This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. 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 (contact the FDA project manager). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to 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.

Following FDA GENERAL COMMENTS, your questions appear in *italics*, followed by FDA's responses in **boldface**.

#### FDA GENERAL COMMENTS

**Our understanding of your current drug development plan in preparation for an NDA is that:**

- A. Sensitivity will be based on GE-067-007 (Study 007) with 31 amyloid-positive subjects on pathology and a success criteria of >70% sensitivity (lower bound of 95% confidence interval [CI]) for at least 3 of the 5 readers (pages 7, 22, 39 of background package).**
- B. Specificity will be based on three separate estimates: (a) 181 young healthy volunteers from GE-067-015 (Study 015) (page 8), (b) at least 15 amyloid-negative brains Study 007 (page 16), and (c) 35 amyloid-negative samples from GE-067-008, GE-007-009, GE-007-010, and GE-067-011 (Studies 008, 009, 010, and 011) (pages 14, 16, 22 of background package). You do not plan to explicitly state success criteria for specificity (page 22 of background package). However, you plan to report the 95% CI for Study 015.**

**C. Based on FDA's June 20, 2011 Advice Letter, you have added GE-067-020 (Study 020) to validate a remote training program for teaching visual evaluation of F-18 flumetamol PET images to nuclear medicine physicians. You apparently are proposing to allow readers to choose either (or both) a color or gray scale for visual interpretation of PET images (the study outline does not describe the procedure but page 18 appears to indicate that training will be provided in both color and gray scale and readers will be trained to read both types of presentations).**

**The Agency places a heavy emphasis on Study 020 because this study incorporates a clinically applicable compact disc training program rather than a "hands on" training program. As a result, our emphasis on Study 020 is for efficacy verification, and for labeling/clinical implementation guidance.**

**Regarding the design of Study 020, we emphasize the importance of an appropriate composition of subjects whose images are interpreted. In particular, we strongly encourage (a) that you include all available subjects who have had an autopsy (Study 007) and truth standard at the time you start Study 020, and (b) that you also bolster the amyloid-negative population with the 35 amyloid-negative individuals with biopsy from Studies 008, 009, 010, and 011. For further comments on Study 020, see FDA Response 2 below.**

**Regarding the label, we anticipate that results from clinical studies that most closely resemble how health care professionals might use your product, if approved, would be placed in the label.**

***GE Question 1:***

*The Division recommended that GE Healthcare try to produce a subject-level sample size sufficient to reliably estimate sensitivity and specificity of the imaging test relative to the histopathology standard. GE Healthcare believes the proposed autopsy study [(GE-067-007)] will provide a reliable estimate of the sensitivity of Flutemetamol F 18 Injection and that the results from [Study GE-067-015] (healthy volunteers) will provide a reliable estimate of the specificity of Flutemetamol F 18 Injection. The specificity estimate will be augmented in the NDA with the results from [Study GE-067- 007] (autopsy) and the pooled results from [GE-067-008], [GE-067-009], GE-067-010, and GE-067-011 (biopsy studies) to provide the Agency reassurance concerning the accuracy of the estimate. Does the Agency agree?*

**FDA Response 1:**

**Not fully. Regarding subject-level sensitivity and specificity estimates, the Agency also places heavy emphasis on the results of Study 020. See FDA General Comments above.**

***GE Question 2:***

*GE Healthcare would like to discuss the accompanying protocol synopsis (GE-067- 020) for evaluating the "hands off" training materials for image reader training, i.e. the proposed CD validation read. Based upon the Agency's comments, the Division recommends including representative images from Studies GE-067-007 (autopsy study), GE-067-005 (MCI and probable AD patients), GE-067-015 (young healthy volunteers) and ALZ201 (probable*

*Alzheimer's disease patients and elderly healthy volunteers). GE Healthcare believes that the proposed study would provide the necessary data to determine if the proposed training materials will be successful in the marketplace. Does the Agency agree?*

**FDA Response 2:** It is premature to fully answer this question based on a protocol synopsis. Based on the synopsis provided, we strongly encourage (a) that you include all subjects who have undergone autopsy in Study 007 at the time you start Study 020, and (b) that you include the 35 amyloid-negative subjects from Studies 008, 009, 010, and 011 to increase the number of amyloid-negative subjects with histology. We agree with including a high proportion of subjects with MCI given that this is the likely intended population for your drug. In fact, we recommend inclusion of more than 40 MCI subjects from Study 005 into Study 020. We also encourage inclusion of a higher proportion of elderly healthy volunteers because these individuals may have a higher likelihood of being amyloid-negative, and because a negative scan result is clinically meaningful whereas a positive scan result is not.

We encourage you to submit the full protocol for Study 020 for review prior to finalizing. We have the following additional comments as you develop your full protocol:

1. Provide a detailed description of the training process and clarify the numbers of the teaching cases and self-assessment cases.
2. Confirm that the images used in the training the readers will not be re-used in the blinded image evaluation.
3. As stated in our General Advice letter of June 20, 2011, we reiterate that inclusion of too many young healthy volunteers will likely cause specificity to be biased high. If you include young healthy volunteers, we continue to recommend an additional analysis of the young healthy subpopulation.
4. Justify your pre-specified Fleiss' kappa value 0.60 for the inter-reader agreement analysis.
5. We recommend that the success criteria for sensitivity and specificity be that the *same* 7 out of 9 readers achieve pre-specified thresholds for the lower bounds of the 95% confidence interval for both sensitivity and specificity. Clarify your calculation of sensitivity and specificity (i.e., identify the relevant populations). We assume the sensitivity will be based upon patients with a pathology truth standard; we are less clear on the specificity population. For example, you may intend to include some young healthy volunteers in the specificity population.
6. Regarding Study 005, clarify the number of MCI subject enrolled so far, and the number of MCI subjects with the PET images. Given that individuals with MCI will likely be the intended population, we recommend an additional analysis of inter-reader agreement for this sub-group. As stated above, we also recommend inclusion of more than 40 individuals with MCI into Study 020.

7. **Clarify if the confidence measurement with scores of low, medium and high proposed in the Study 007 will also be performed in Study 020.**
8. **You have planned for 9 readers; we would not regard a smaller number (such as 5) as unreasonable.**
9. **We are concerned that your reader training methods, which appear to allow either gray scale or color may complicate the reading process since the data will need to substantiate the recommendations we anticipate for labeling. If you allow both options, plan to include analyses that verify the gray/color option does not compromise sensitivity/specificity/agreement.**
10. **Page 21 appears to indicate that readers will be chosen from persons with medical degrees (as the sole criterion). Clarify that the readers will be representative of clinicians who would actually report the scans in medical practice (for example, physicians with training in nuclear medicine/not family physicians or pediatricians).**

***GE Question 3:***

*The Division suggested that GE Healthcare should develop a computerized program that allows accurate and reproducible image interpretation and that the acceptability of this training process would need to be assessed in a premarket study. Although this validation study will provide estimates of sensitivity and specificity, GE Healthcare proposes that the values of sensitivity and specificity determined in our principal Phase 3 clinical trials (GE-067-007 and GE-067-015) should be presented in the label rather than those from the training validation. Does the Agency agree?*

**FDA Response 3: No. Please see FDA GENERAL COMMENTS above. As you know, most labeling statements are contingent upon study results. At the present time, we envision the Study 020 outcome as appropriate for consideration within labeling.**

***GE Question 4:***

*The Division inquired as to the dose that GE Healthcare will be recommending in its labelling for Flutemetamol F18 Injection. In its responses to the Agency, GE Healthcare has explained that the recommended dose will be 185 MBq (5mCi). Does the FDA agree with this recommended dose?*

**FDA Response 4: It is premature for us to comment on the recommended dose for the label without considering the totality of the dose information once all studies are completed. Additional information to be considered includes:**

**The number of subjects administered 5 and 10 mCi in Study 007 (and other studies if there are different doses administered) and the imaging times.**

**How image quality is assessed and deemed to be comparable among different doses and imaging times.**

**We are perplexed about why the duration of PET imaging in Study 007 in individuals administered 5 mCi is approximately 30 minutes (page 131) given that Table 3 on page 20 appears to indicate 10 minute PET scan duration for 5 mCi in studies 015 and 005. Please clarify.**

**FDA Additional Comments:**

- 5. Page 140. For Study 007, it appears that visual interpretation of PET images will be made for “both hemispheres separately.” Clarify what the subject-level interpretation will be if the interpretation for the two hemispheres for the same subject do not agree.**
- 6. Page 16. It appears that 28 of the 35 amyloid-negative samples from biopsy studies have results based on Bielschowsky silver stain. Clarify the pathology method used on the other 7 amyloid-negative samples from biopsy studies, the reliability of that method, and whether it would be possible to perform Bielschowsky silver stain on these other 7 samples.**
- 7. For samples from biopsy studies, clarify how the samples are obtained (including the number of brain regions biopsied and the number of samples per individual), and how much tissue is in each sample. If this information is in a previous submission with the protocols for Studies 008, 009, 010, and 011, please provide the date of submission(s).**
- 8. Provide the Injected Activity and PET scan duration used for the biopsy studies (Studies 008, 009, 010, 011) in a table resembling Table 3 on page 20.**
- 9. Page 21. We question that imaging medical physicists represent clinical practitioners in the United States (U.S.). Please comment. If not, we recommend replacing imaging medical physicists with readers who may likely read F-18 flumetamol PET images in clinical practice in the U.S. or perform a subset analyses for the 7 nuclear physicians for Phase 3 studies.**
- 10. Page 21. Your response to our previous question 9 appears to suggest that Phase 3 studies have thus far used 9 readers (7 nuclear physicians and 2 imaging medical physicists). Yet in protocol for Study 007 (e.g. Synopsis on page 36), you state “5 independent, trained readers...” are used. Clarify this discrepancy.**
- 11. Page 139. Clarify how you plan to use the immunohistochemistry data in the analysis. Do you plan to use a correlation or set a threshold for positive versus negative?**

# ATTACHMENT 2

## GEHC Summary of Understanding

### Flutemetamol F 18 Injection (IND 101866)

#### FDA Meeting 25 October 2011

We thank the FDA for providing a preliminary response to our questions in advance of our scheduled teleconference, which we always find most helpful. The following is our summary of understanding for your review and we plan to use this summary as the basis for our discussion today.

#### A) GE - 067 - 020

The FDA has placed a great deal of focus on the GE 067 020 study and we understand this to

mean that emphasis will be placed on Study 020 for efficacy verification and labeling guidance.

The two tables below summarize the revised cohorts in Study 020 for a) sensitivity and

specificity and b) reader agreement/reproducibility. Although listed as separate cohorts in

these tables, the images will be read as one dataset, individually randomized for each reader.

<b>Study GE - 067 - 020: Sensitivity and Specificity Analysis (Validity)</b>						
<b>Study GE - 067 -</b>	<b>Phase</b>	<b>Sample Size</b>	<b>SOT</b>	<b>SOT Positive for Sensitivity</b>	<b>SOT Negative for Specificity</b>	<b>Comments</b>
007 Autopsy	3	62 (current estimate)	Bielschowsk y stain	at least 31	at least 22	all available brains from Study 007 will be included in Study 020
009, 010, 011 Biopsy	3	36	Bielschowsk y stain	8	28	biopsy Study 008 (n=7) omitted as

						tissue not available for Bielschowsky staining
015 YHV	3	31	Assumed negative	none	31	31 images randomly selected from a total of 181 – we believe this is sufficient for a stand alone subanalysis without creating a bias to the overall specificity analysis
Total		129		at least 39 (all with histopathology)	at least 81 (at least 50 with histopathology)	

Study GE - 067 -	Phase	Sample Size	Population	Comments
007 Autopsy	3	62 (current estimate)	62 end of life	all available brains from Study 007 will be included in Study 020
009, 010, 011 Biopsy	3	36	36 – normal pressure hydrocephalus	biopsy Study 008 (n=7) omitted for kappa
015, YHV	3	31	31 – young healthy	31 images randomly selected from a total of 181
005	3	60	60 – mild cognitive impairment	60 images randomly selected from a total of 231 (from multiple sites) – in response to FDA request for

				additional MCI images
201	2	55	20 – mild cognitive impairment 15 – elderly healthy 20 – probable AD	55 images selected from a total of 72 – includes all MCI and elderly healthy volunteers and 20 probable AD; excludes all young healthy volunteers and 7 probable AD (lower dose given for test retest)
103	1	10	5 – elderly healthy 5 – probable AD	10 images selected from a total of 22 – includes all elderly healthy volunteers and probable AD scanned with equivalent scan times
014	1 (Japan)	16	8 – elderly healthy 8 – probable AD	16 images selected from a total of 22 – includes all elderly healthy volunteers and probable AD scanned with equivalent scan times
Total		270	62 – end of life 36 – normal pressure hydrocephalus  31 – young healthy  80 – mild cognitive impairment  28 – elderly healthy  33 – probable AD	

**Question for FDA: Does the FDA agree Study 020 is pivotal for deriving both sensitivity and specificity, as well as for the determination of reader agreement as measured by kappa? If yes, shall we assume these data will be included in the label?**

In reading your preliminary response we noted several questions pertaining to Study 020 and can provide the following responses:

1. Visual interpretation of Flutemetamol images will be via a color scale only. This also applies to the CD training program.
2. Images used in the training of readers will not be used in the blinded image evaluation
3. Reader confidence measures with scores of low, medium and high will be performed, in accordance with all Flutemetamol reads to date.
4. All readers will be board certified in nuclear medicine or radiologists with training in nuclear medicine.
5. Unlike the autopsy study, no secondary endpoint of immunohistochemistry for correlation analysis will be included.

### **B) Flutemetamol Clinical Study Reports**

All Flutemetamol clinical study reports, except for Study 020, will report data based upon the original "hands on" reader training. We do not expect to amend these reports once the "hands off" re-read data from Study 020 are available.

Furthermore, the clinical study report for Study 005 will be an interim report of final safety and kappa results only, as this is an ongoing phase 3 study that is intended to support label expansion, post approval.

Lastly, the individual clinical study reports for the phase 3 studies 007, 015, and 005 include reader kappa scores from a total of 5 readers, 4 nuclear medics and 1 imaging medical physicist (not the exact same readers across studies). For the phase 3 biopsy studies 008, 009, 010, and 011 the reader kappa scores were derived from a total of 3 readers, 2 nuclear medics and 1 imaging medical physicist (also not the exact same readers across studies). Although we don't intend to replace the imaging medical physicists used in these studies, in light of the fact that these data will not be reflected in the labeling, we will ensure the planned Study 020 will use only readers who are board certified in nuclear medicine or radiologists with training in nuclear medicine.

**Question for FDA: Does the FDA accept this approach for the NDA?**

**C) Number of Readers in Study 020**

In light of the FDA feedback we are considering reducing the number of readers in Study 020 from 9 to 5, which will then be consistent with the blinded read evaluations from 007, 015, and 005 (which have all used 5 readers, as mentioned above). The criterion for success will be that the null hypothesis is rejected for at least 3 of the 5 readers, and we would propose to report the individual results from all 5 readers in the label.

**Question for FDA: Does the FDA agree with this approach?**

**D) Dose/Acquisition Time**

In Study 020, the autopsy data obtained at 370 MBq injected will be read with a 10 minute image time. Equivalently, all other data were obtained at 185 MBq and will be read with a 20 minute image time. We believe this clarifies our position with respect to dose and image time and intend to propose a dose of 185 MBq and a 20 minute scan time in the label.

**E) Response to FDA Questions about Autopsy Study**

In reading your preliminary response we noted several questions pertaining to Study 007 autopsy and can provide the following responses:

1. For visual interpretation, a global assessment of the brain was considered rather than individual hemispheres. Our statement on page 140 (GE 067 007 A02) of the briefing document is incorrect and relates to a strategy which GEHC has not pursued for any studies in the clinical development program. The image review charter for this study asks the reader to navigate between both hemispheres to gain a global assessment therefore, the wording in the protocol is incorrect and a deviation will be recorded.
2. Immunohistochemistry data are used for a correlation analysis, which is a secondary endpoint. We plan to analyze a total of 30 brains for

correlation. As immunohistochemistry is not accepted as a part of CERAD, it was not chosen as the SOT for primary analysis.

3. In CERAD, Bielschowsky silver staining is routinely accepted and is more stable than other amyloid stains, such as thioflavin S. It has therefore been chosen for the primary SOT analysis, with a threshold set based upon a cut off score of 1.5 (i.e., a measure between CERAD sparse and moderate).

#### **F) Response to FDA Questions about Biopsy Studies**

In reading your preliminary response we noted several questions pertaining to the biopsy studies (008, 009, 010, 011) and can provide the following responses:

1. After preparation of microscope slides with other stains, there was not enough brain tissue remaining to perform Bielschowsky silver staining analysis for Study 008; we therefore intend to exclude this study from the Study 020 analyses.
2. One brain biopsy sample was taken per subject. The brain region biopsied was in line with local clinical practice where applicable, and was frontal cortex for Studies 008, 010, and 011 and parietal cortex for Study 009.

Please note we plan to submit the final protocol for Study 020 to the FDA for review within the next 4 weeks. The remaining comments/questions posed by the FDA from its preliminary response will be addressed in this protocol. As this protocol is on critical path, we would appreciate FDA feedback within 30 days of receipt.

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/s/  
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SHARON P THOMAS  
11/22/2011



IND 101,866

ADVICE/INFORMATION REQUEST

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [<sup>18</sup>F] Flutemetamol Injection.

We also refer you to your submissions dated February 11, 2011 and April 8, 2011.

We have reviewed the referenced material and have the following comments to your questions: Your questions are in *italic* and our responses are in **boldface**.

**FDA General Comments:**

- I. **We strongly disagree with your proposal to base your primary specificity determination solely on young healthy volunteers without histopathology. We strongly encourage continuation of the autopsy study in order to try to produce a subject-level sample size sufficient to reliably estimate sensitivity and specificity of the imaging test relative to the histopathology standard. We strongly advise continued efforts to obtain autopsy information throughout premarketing development. The basis for our concern is outlined below.**
  
- II. **We reviewed the protocols and associated documents for GE-067-007 and GE-067-015 in light of the discussions from the January 2011 advisory committee meeting. We have the following comments for you to consider as you further refine your plans. At the January 20, 2011 advisory committee discussion of another amyloid imaging agent, the following points were cited as especially important in the development of these types of products:**
  - a. **The image interpretation process for clinical (market) use of the drug needs to be established in premarket studies. We favour the use of training materials that do not necessitate person to person, on-site interaction with instructors (instead, we favour a computerized format). For example, a sponsor may choose to use a format (such as computerized training/DVD/CD) that provides the nuclear medicine physician with information necessary to accurately and reproducibly read the**

images without any need for “hands on” training and certification. We generally anticipate that training materials would be handled by FDA in a manner similar to other marketing materials in the post-approval setting.

- b. In general, we have anticipated that sponsors would not desire to use a reading process that necessitates reader “certification” based upon “hands on” training similar to what you have proposed for your phase 3 study. The ability to easily translate a validated reader training program into clinical practice is an important consideration. While we do not object to the reader certification process you have proposed for your phase 3 study, please be aware that we generally expect that you develop a less intense reader training process (e.g., a computerized program that describes key image interpretation characteristics, image examples and a self-contained exercise on example images) that allows accurate and reproducible image interpretation. The acceptability of this less intense reader training process would need to be assessed in a premarket study that examined (at least the following):
- sensitivity/specificity of image interpretations with respect to the histopathology standard of truth (or, for specificity, inclusion of healthy volunteers who putatively lack amyloid if insufficient autopsies are available from patients who lack amyloid). We note that including young healthy volunteers in the study sample will likely cause specificity to be biased high. If it is impossible to estimate specificity without using young healthy volunteers, an additional analysis of the young healthy subpopulation should be done so that it can be identified as such and included in the label.
  - agreement/reproducibility of image interpretations within and across readers (intra and inter-reader agreement) who examine images from
    - i. the population with histopathology standard of truth, and
    - ii. a clinically applicable patient population (e.g., patients with early signs/symptoms of dementia, mild cognitive impairment, probable Alzheimer’s disease, older healthy volunteers). Studying the clinically appropriate population will also tend to minimize the spectrum bias caused by reading the extremes of the spectrum of disease which would likely result in inflated performance estimators. We encourage evaluation of agreement for images from the older healthy adults based on their higher likelihood of a negative scan and the clinical utility of a negative scan.

Alternatives to a “less intense, computer based” reader training process may be reasonable and, if hands-on tutorials with reader “certification” are essential for accurate and reproducible image interpretations, then we wish to further discuss this necessity.

**III.** You may wish to consider the concepts outlined above (item II.) as you refine your phase 3 protocol, independent reading charter, and statistical analysis plan. We express our concerns because the January 2011 advisory committee discussion

**illustrated the potential for successful completion of a phase 3 study yet the phase 3 study provided insufficient support to allow clinical implementation of the imaging test.**

**Consequently, you may wish to address the concepts outlined above within a subsequent study that incorporates images from patients who have undergone autopsies and patients with a spectrum of cognitive impairment. In essence, this subsequent study would pool the multiple image data in a manner that uses a clinically-applicable subject-level reader training process and a clinically meaningful histopathological threshold for amyloid to assess the test sensitivity (among patients with amyloid on autopsy), specificity (among patients without amyloid at autopsy and possibly presumptively amyloid-negative volunteers) and reader agreement (intra- and inter-reader) of images across a clinically-applicable spectrum of patients (as well as within subsets of patients). To clarify, the reading queue for image interpretation would include images from subjects with and without histopathology randomized together (e.g. from GE-067-007, GE-067-005, and possibly from GE-067-015). We anticipate the need for protocol-specified success criteria for this study as well as submission of the reader training material (as feasible).**

**IV. We strongly disagree with your use of anatomic images to aid readers for the primary analysis in GE-067-007. As stated in II.a. above, premarket studies should establish the image interpretation method for clinical use. Given that you believe anatomic images will not be necessary in clinical practice, we disagree with your proposal to use anatomic images in a pivotal premarket trial. We find it unlikely that the indicated population will not include patients with brain atrophy. If you find in a pilot study that anatomic images are necessary for flumetamol PET image interpretation for subjects with atrophy, then (a) you should plan to require the acquisition and use of anatomic images for reading PET amyloid images in clinical practice and (b) the training program you plan to implement in clinical practice should include training on extracting key information from anatomic images and the method should be established in the Phase 3 trial. Use of anatomic images in the Phase 3 trial(s) will also necessitate reflection in the label.**

**V. We recommend that you consider recruiting end-of-life subjects without restriction to memory clinics in order to obtain a reasonable number of autopsy subjects who are “negative” for amyloid. We suspect that subjects recruited from memory clinics may have a higher probability of being “positive” for amyloid on histopathology. Yet autopsy subjects “negative” for amyloid are equally important to include in your primary analyses. In addition, end-of-life subjects with a short life expectancy due to non-memory causes (e.g. cancer, heart disease) may have less atrophy, which may obviate the use of anatomic images as an aid for reading PET amyloid images.**

*Question 1:*

*Does the FDA agree that, subject to the data being obtained, the proposed clinical development plan can support the following proposed indication claim?*

**FDA Response 1: No. See general comments above.**

*Question 2:*

*Does the FDA agree that our plans to provide data from the Phase 3 prospective autopsy study (GE-067-007; to estimate sensitivity) and the Phase 3 prospective study in healthy young adults (GE-067-015; to estimate apparent specificity) are acceptable to establish the validity of the visual interpretation of [18-F]flutemetamol images in detecting or excluding the presence of fibrillar A $\beta$  in the brain?*

**FDA Response 2: No. See general comments above.**

*Question 3:*

*Does the FDA agree that the autopsy study GE-067-007 is complete when the Independent Data Monitoring Committee for pathology (IDMC-P) declares that at least 22 brains that are positive for fibrillar A $\beta$  (and for which there are evaluable PET images) have been obtained and that the final number also includes other brains that have been collected prior to formal study termination?*

**FDA Response 3: No. See general comments above.**

**For subjects with histopathology, we recommend that you determine a sample size that can reliably estimate both sensitivity and specificity.**

**Justify your assumption that true sensitivity is (b) (4).**

*Question 4:*

*Following a literature review showing that significant levels of fibrillar A $\beta$  are exceedingly rare in the brains of cognitively intact adults under the age of 40 years, GE Healthcare does not believe it is necessary to conduct ApoE4 genotyping of subjects in the healthy young adult study, and therefore "all comers" will be included in the primary efficacy analysis for this study. GE Healthcare welcomes the FDA's perspective on this.*

**FDA Response 4: If you determine that you must include young healthy volunteers in your primary specificity pool, we generally agree with not imposing an ApoE4 criterion for enrollment of young healthy adults who do not have a 1<sup>st</sup> degree relative with AD. However, we point out that if a young healthy volunteer is amyloid "positive" on imaging and assumed to be "negative" on truth, then the specificity estimate may be lowered even though classification of this subject as a false positive may be in error.**

*Question 5:*

*Does the FDA agree with GE Healthcare's plan to supplement the blinded read of the [18-F]flutemetamol scans from the healthy young adult study with positive and negative [18-F]flutemetamol scans from a clinically relevant patient population by conducting concurrent reads of PET images from the amnesic mild cognitive impairment study GE-067-005 and the healthy young adult study, and that this approach aligns with the read process which will be used in clinical practice?*

**FDA Response 5: See FDA general comments above (particularly III.) and FDA comment 8 below.**

*Question 6:*

*Does the FDA agree with the size of the overall safety database supporting the registration of Flutemetamol F 18 Injection?*

**FDA Response 6: Yes, we generally agree.**

**Additional Comments from Division:**

**7. Histopathology:**

- a. **Justify your use of only one histopathologist for determining the CERAD score used as the standard of truth (SoT) for your primary analysis.**
- b. **Our understanding of your method to determine the CERAD score which serves as the SoT for your primary endpoint in GE-067-007 is as follows. Two samples from each of 8 brain regions will be sampled. Each sample will yield 50 sections, and silver staining will be performed on 4 of the 50 sections per sample. Since there are 2 samples per brain region, there will be 8 samples per region for which the number of neuritic plaques are counted and converted into a GE-067 Grade Score (4-point scale from 0 to 3) as in Appendix 2 of the Histology Study Plan. The GE-067 Grade Scores from these 8 samples are averaged, and if this average is  $\leq 1.5$  then a “normal” classification is assigned for the region. Clarify if our understanding is correct.**
- c. **Provide an explanation for how the subject level classification of normal or abnormal is assigned based on the region level classification of the mean GE-067 Grade Scores.**
- d. **Justify your choice of 1.5 (regional mean) as the threshold for normal versus abnormal in the modified CERAD semi-quantitation scheme. Clarify if the chosen**

**threshold corresponds to any particular number of plaque counts (e.g. 9 to 10 per field).**

- e. Clarify the degree to which immunohistochemistry (4G8 staining) is automated.**

## **8. Dose**

- a. Clarify the dose you plan to use in clinical practice if flumetamol is marketed. This anticipated dose should be the dose whose efficacy and safety are established in the Phase 3 trial(s).**
- b. We note your proposal to administer 185 to 370 MBq in GE-067-007 based on whether subjects can tolerate 30 minutes of PET imaging. We are concerned about the image quality of a 10-minute PET scan using the 370 MBq dose. We note that your single Phase 2 study and all of the other 6 Phase 3 studies use only the 185 MBq dose. Provide data to support (a) the adequacy of images obtained using 370 MBq and a 10 minute scan and (b) the higher radiation dose from the 370 MBq administration.**

## **9. Image interpretation**

- a. Justify the use of the color scale versus gray scale.**
- b. We recommend that you propose criteria for selecting image readers for your Phase 3 trials such that they would be representative of individuals anticipated to read amyloid PET images in clinical practice in the U.S. We question the frequency with which individuals without a medical degree would read amyloid PET images in clinical practice in the U.S.**

## **10. Analyses**

- a. Propose success criteria, and justification, for both sensitivity and specificity in the primary analyses.**
- b. We strongly discourage the use of majority reading when evaluating your drug. Since it is unlikely that majority reading will be the standard in clinical practice, the sensitivity and specificity estimates provided under such a study would not be representative of the performance under intended conditions of use. Please consider revising your performance study to more closely mimic clinical practice.**
- c. Uninterpretable is subjective. The number of images that are uninterpretable will change with the reader. Allowing an uninterpretable classification will likely bias high both sensitivity and specificity estimates. We understand that some equipment malfunctions or gross subject movement may absolutely cause an image to be uninterpretable.**

- i. **Pre-specify detailed criteria for un-interpretables. These criteria will be a review issue.**
  - ii. **Provide an estimated percentage of missing and/or un-interpretable images.**
  - iii. **Propose a method to avoid bias using only available data without un-interpretable images / missing values.**
- d. **Provide detailed methods for intra- and inter-reader variability analyses.**
- e. **Based on the review charter, readers will assign to each image set a “confidence score” from 1 to 5. Clarify the analysis plan using the “confidence score.”**
- 11. Anaphylactoid reaction: Comment on the association of Polysorbate 80 with allergic reactions based on the literature and on adverse event reports for other GE products that contain Polysorbate 80.**
- 12. The INDICATION(S) on Form 1571 (category 7) states, “*Diagnostic radiopharmaceutical for targeting angiogenesis associated with primary and metastatic cancer*”. Clarify if this is a typographical error.**

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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**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  
06/20/2011



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** EOP 2-Pre-phase 3  
**Meeting Date and Time:** September 7, 2010 2:00 pm- 3:00 pm  
**Meeting Location:** White Oak, Conference Room 1417

**Application Number:** IND 101,866  
**Product Name:** Flutemetamol F 18 Injection  
**Indication:** PET imaging for detecting brain  $\beta$ -amyloid deposition  
**Sponsor/Applicant Name:** GE HealthCare

**FDA ATTENDEES:**

Charles Ganley, M.D., Office Director, ODE IV  
Rafel Dwaine Rieves, M.D., Division Director, DMIP  
Alex Gorovets, M.D., Primary Clinical Team Leader, DMIP  
Libero Marzella, M.D., Clinical Team Leader, DMIP  
Qi Feng, M.D., Primary Clinical Reviewer, DMIP  
Jyoti Zalkikar, Ph.D., Statistical Team Leader, DMIP  
Lan Huang, Ph.D., Primary Statistical Reviewer, DMIP  
Sally Hargus, Ph.D., Pharm/Tox Reviewer, DMIP  
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader, DMIP  
Christy John, Ph.D., Clinical Pharmacology Reviewer, DMIP  
Ross Felice, M.D., Clinical Reviewer, DMIP  
Chekesha Clingman, Ph.D., Clinical Reviewer, DMIP

**SPONSOR ATTENDEES:**

Christopher Buckley, PhD, Technology Project Manager  
Yamo Deniz, MD, Global Head of Clinical Development  
Kevin Horgan, MD, Head of Internal Medicine  
Igor Grachev, MD, PhD, Clinical Project Leader  
Allison Mueller, Head of Americas, Regulatory Affairs  
Gill Farrar, PhD, Project Director  
Marisa Coyle, Manager, Regulatory Affairs

**1.0 MEETING OBJECTIVES:**

To discuss the FDA's draft comments sent to the sponsor on September 3, 2010.

**2.0 BACKGROUND:**

GE HealthCare requested an End-of-Phase 2 meeting on May 20, 2010, to discuss their Phase 3 clinical development program for Flutemetamol. Flutemetamol F 18 Injection is a positron emission tomography (PET) imaging indicated for the visual detection of brain fibrillar A $\beta$  deposition.

On September 3, 2010, FDA provided responses to the sponsor's questions submitted in their August 5, 2010 briefing package (Attachment 1). The sponsor decided to proceed with the meeting to discuss their pivotal phase 3 studies and address some of the FDA's comments.

**3.0 DISCUSSION:**

After introductions of the meeting participants, the sponsor proposed to go through their Power Point presentation (Attachment 2).

Summary of Discussion:

*The sponsor provided an overview of their normal pressure hydrocephalus (NPH) biopsy, autopsy, and new Healthy Young Adult studies.*

*As supportive evidence for the biopsy program, the sponsor discussed the virtual biopsy analysis from the phase 2 data, results from the flutemetamol (GE-067-008) biopsy study, and cited a published report from Finland showing a correlation between the biopsy and the global amyloid assessed with [ $^{11}$ C]PIB imaging.*

*FDA explained the importance of studying a diverse cohort and concerned about the homogeneity of the NPH patient group. The sponsor replied that the subjects in the NPH group were routine patients seen in the clinic as opposed to autopsy patients who were terminally ill at the time of PET scanning. The sponsor noted that 468 NPH patients in the Finland study had amyloid deposition. The sponsor stated that the pattern of amyloid seen in the flutemetamol images of NPH patients were not different from patients with Alzheimer's disease.*

*The sponsor noted that the data would be merged in an integrated visual read analysis with data from a study of young healthy volunteers using the same terminology. FDA requested the integrated results and data from the Young Healthy Adult study and asked the sponsor to clarify the retrospective and prospective biopsy data in a future submission. FDA discussed the potential risk*

*of biopsy sampling and requested the sponsor to provide reliable standard of truth estimates.*

*FDA inquired about the additional use of autopsy data to demonstrate the relevance of biopsy sampling to the global amyloid assessment. FDA stated that the numbers collected for autopsy study so far was insufficient for sensitivity or specificity. The sponsor inquired about the possibility of adding autopsy data into the integrated visual read analysis along with the data from the biopsy and healthy young adult study. FDA requested the sponsor to provide the rationale and methodology in a future submission.*

*FDA suggested that the sponsor not perform the Healthy Young Adult study at a single center and requested that scans come from different centers. FDA suggested a higher recruitment number with a sample size of 100-300 for specificity test of the investigational agent.*

*The sponsor inquired if would be acceptable to combine data from the biopsy, autopsy and Healthy Young Adult studies as the primary endpoint for developing sensitivity and specificity. FDA did not agree the pooled analyses plan since the primary endpoints in the NPH and autopsy studies are not same (see FDA response to the question 1e, below).*

*FDA expressed the importance of the labeling language for flutemetamol based on a visual read to provide the imaging physicians with information on how the PET image will be interpreted in clinical practice. The sponsor concurred.*

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# ATTACHMENT 1

## FDA Preliminary Responses

**Introductory Comment:** This material consists of our preliminary response to your questions in preparation for the meeting scheduled for **September 7, 2010** between GE Healthcare and the Division of Medical Imaging Products (DMIP). This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. 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 (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to 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. Your questions are listed below in regular font and are followed by our responses in **bold font**.

### **SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSE:**

Flutemetamol F 18 Injection is being developed to support the following indication:



1. Does FDA accept our approach to having one biopsy and one autopsy study serve as the pivotal studies in support of this indication, with additional data provided as supportive information?

#### **FDA Response:**

- A. We find your overall approach conceptually reasonable but deficient in critical details of the visual assessment methodology and the determination of performance characteristics (especially specificity) on a patient-level. We are unable, from the supplied outline, to infer a method for visual assessment of a patient's image from the regional SUVR measurements proposed by you. This is a major deficiency that must be resolved.**

**Your proposal lacks a clear description of the visual assessment process to determine the presence or absence of amyloid at a patient level. We believe such an assessment would be commonly performed by a practitioner and has to be included in your studies and eventually addressed in the labeling.**

**We do not understand how your primary endpoints, based on the SUVR of isolated cerebral regions, can lend themselves to a useful clinical interpretation of a whole-brain scan in practice. Furthermore, the two proposed biopsy studies appear to rely heavily on the assumption that the presence or absence of amyloid in a relatively circumscribed sample of brain tissue can reliably be extrapolated to a global assessment of cerebral amyloid load. Please clarify whether you make such an assumption and justify it if you do.**

**Discussion: See Discussion Summary above.**

- B. We reserve the comment on the wording of the indication statement until future discussions. However, we note that that the second component of your proposed indication is not appropriate for potential inclusion in future product labeling.**

(b) (4)

(b) (4)

**In remaining consistent with the findings of the October 23, 2008 Advisory Committee Meeting on this topic, any proposed indications for the radionuclide imaging agents for amyloid should relate solely and clearly to the potential utility of a “negative” amyloid test in ruling out a diagnosis of AD.**

**Discussion: See Discussion Summary above.**

- a. Does FDA accept the proposed designs for the above-referenced pivotal studies?

**FDA Response:**

**No, we do not accept the proposed analytical design.**

**According to the AC meeting on 10/23/2008, a “negative” amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer’s Disease (AD) and a “positive” test would have very limited utility since cerebral amyloid is known to be present in multiple conditions, including normal aging. We have previously recommended (see our comment 10.b at the telephone conference of 03-26-09) and we still recommend that you ‘bolster your plans by performing a study that ... assesses specificity within the subset of healthy young adults with presumptively no brain amyloid.’ (We can assume, without histopathology confirmation, that the healthy young adults under 40 years old are amyloid free). The inclusion of a study population widely accepted to be amyloid negative, such as younger healthy subjects, will likely provide much greater support in establishing the false positive rate of Flutemetamol imaging to be low which, as previously stated, will be critical to its ultimate clinical utility.**

**Discussion: See Discussion Summary above.**

- b. Does FDA accept our approach to use quantitative analysis of tracer uptake as the primary endpoint in the pivotal studies?

**FDA Response:**

**Please see comments above.**

**Discussion: See Discussion Summary above.**

- c. Does FDA accept the methodology employed to develop the threshold between abnormal and normal [18F]flutemetamol scans, and the proposed threshold between normal and abnormal <sup>(b) (4)</sup> levels based on immunohistochemistry (4G8, plaque % area)?

**FDA Response:**

**Whereas we generally agree with the proposed analytical methodology for the proposed endpoints we do not understand its relationship to the assessment of Flutematol images in clinical practice.**

**Regarding the basis for the proposed threshold, we question whether a SUVR threshold generated in one relatively small trial is applicable across different trials and differently obtained data.**

- d. Does FDA accept the standard of truth (tissue <sup>(b) (4)</sup> levels determined by immunohistochemical [primary] and histochemical [secondary] methods) in each of the pivotal studies?

**FDA Response: Yes.**

**Discussion: See Discussion Summary above.**

- e. Does FDA accept the statistical analysis plans and sample size proposed for the pivotal studies? Specifically, we plan to conduct a pooled analysis of 30 samples from two identical biopsy studies (one US IND study and one ex-US non-IND study) and an analysis of up to 26 tissue specimens/brain from at least 3 brains from an autopsy study that will be on-going during review and approval of Flutemetamol F 18 Injection.

**FDA Response:**

**A. No, we do not agree with your plan for pooled analyses. The primary endpoints in the two biopsy studies and the autopsy study are not the same. There are up to 26 SUVR values per subject in the autopsy study (GE-067-007). However, there is only one value per subject in the biopsy studies (009 and 011). The tissue location, size, type and shape are different for the two types of studies. The patient population is also different in the two types of studies (subjects with short life expectancy for 007 and Normal Pressure Hydrocephalus patients for 009 and 011). It is not appropriate to conduct the pooled analysis of all three studies. Please note that it is acceptable to pool the data for the two biopsy studies 009 and 011 because the only difference in the**

**protocols is the location. For the pooled analyses of 009 and 011, exploration should be conducted for the center effect.**

***Discussion: See Discussion Summary above.***

**B. The sample size in GE-067-007 trial is too small for assessment of sensitivity and specificity. Please justify your expectation that only three subjects (out of the planned 100 who will be imaged) will be available for efficacy analyses.**

***Discussion: See Discussion Summary above.***

2. Does FDA accept our proposal of a pooled analysis of all Phase 3 data (pivotal and supportive), as well as the methodology of analysis, to support visual interpretation of images to be included in the labeling?

**FDA Response:**

**No, we do not agree to the proposed pooled analyses given the differences in the primary endpoints and patient population, as indicated above. Please also see our earlier comments on visual assessment of images.**

***Discussion: See Discussion Summary above.***

3. Having demonstrated that [18F]flutemetamol and [11C]PiB have comparable imaging properties, does FDA agree that [11C]PiB imaging and autopsy data can be used as supportive data for the registration submission for [18F]flutemetamol ?

**FDA Response:**

**We recognize the value of C-11-PIB data as supportive but are compelled to remind you that such data do not provide independent substantiation of your drug's efficacy.**

***Discussion: See Discussion Summary above.***

4. Does the FDA agree that the overall safety database for initial registration is acceptable (at least 300 subjects)?

**FDA Response:**

**Based upon the available data, we generally agree. Please be aware that accumulating data (e.g., new safety concerns or important changes in the targeted indication) may necessitate an increase in the targeted safety database sample size.**

***Discussion: See Discussion Summary above.***

**Additional FDA Comments:**

- **For study 007, an interim analysis will occur when sixty percent of the planned subjects are available for autopsy. If there are only three subjects available for autopsy, the between variation may not be estimable in the mixed model for the primary endpoint. Please clarify the expected study duration which will assure you of obtaining enough cases for autopsy.**
- **To potentially increase the evaluable sample size in the autopsy study, you may wish to increase the time interval between PET imaging and autopsy (e.g. up to six months).**
- **Please clarify your methodology for handling missing data. What is the possible rate of missing observations?**
- **In the Study Design section of the synopsis of Study GE-067-007, you refer to the fact that a blinded visual assessment will be performed by three independent readers, however, there is no further mention of this in the description of the Statistical Methods and Planned Analysis. Please clarify.**

**4.0 DECISIONS REACHED and ACTION ITEMS:**

- **GE will submit a revised protocol when ready.**

## **ATTACHMENT 2**

Presentation Slides: End-of-Phase 2 Meeting - GE HEALTHCARE

# GE HEALTHCARE

## Flutemetamol F 18 Injection End-of-Phase 2 FDA Meeting

September 7, 2010

### Agenda

1. Summary of our understanding of FDA guidance
2. Revised clinical plan addressing guidance
3. Gain agreement on revised clinical plan

## FDA Guidance to GEHC

-appropriate indication:

(b) (4)

- 3 brains from autopsy study insufficient to estimate between subject variation in primary mixed model analysis
- autopsy data cannot be 'pooled' with biopsy data
- bolster plan with healthy young adult study to support specificity of the agent
- biopsy acceptable provided reliable extrapolation to a global assessment of cerebral amyloid load

<sup>3</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Biopsy can be reliably extrapolated to a global assessment of cerebral amyloid load

### Clinical

- Clinicians use frontal cortical biopsy assessment of amyloid as prognostic indicator
  - Series of 433 patients in press:
    - Leinonen et al. Annals of Neurology; in press.

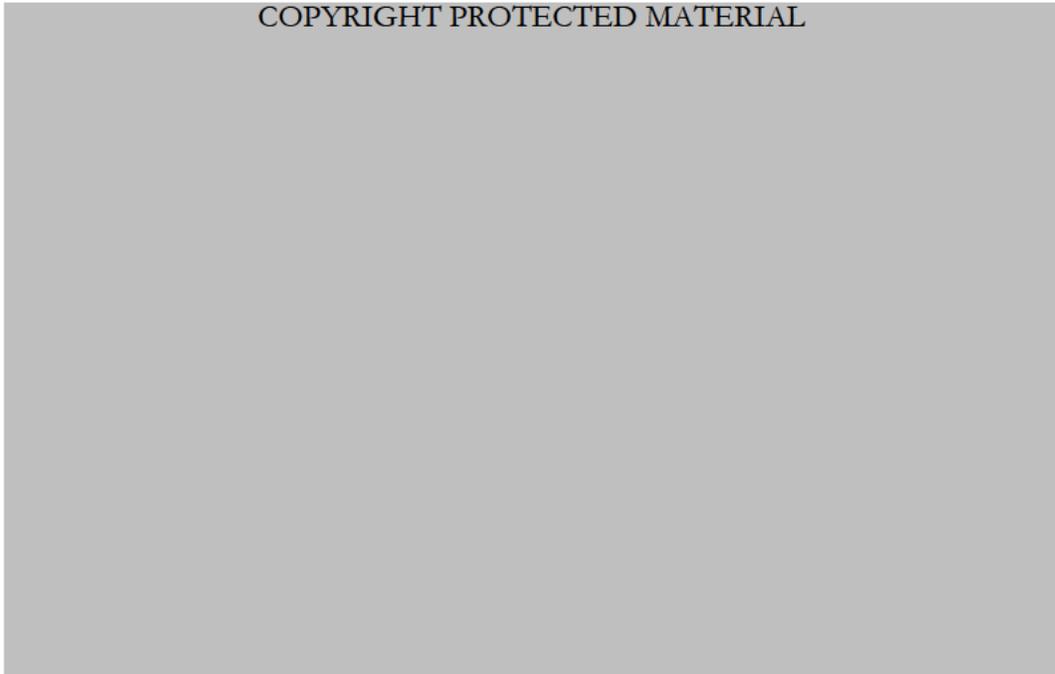
### Pathology

- Frontal lobe early site of fibrillar amyloid deposition and correlates with global cortical amyloid load
  - Naslund et al. JAMA 2000; 283:1571-1577.
  - Nelson et al. Neurosci Letters 2009; 450: 336-339.

### Imaging

- Close correlation between imaging signal from frontal cortical biopsy region and imaging signal derived from other cortical regions where amyloid is typically deposited in Alzheimer's disease
  1. **[<sup>11</sup>C]PiB imaging Biopsy Study:**
    - Leinonen et al. Arch Neurol. (2008) 65(10):1304-9.
  2. **Flutemetamol imaging: "Virtual biopsy" analysis of study ALZ201**
  3. **Flutemetamol imaging: Biopsy study GE-067-008**

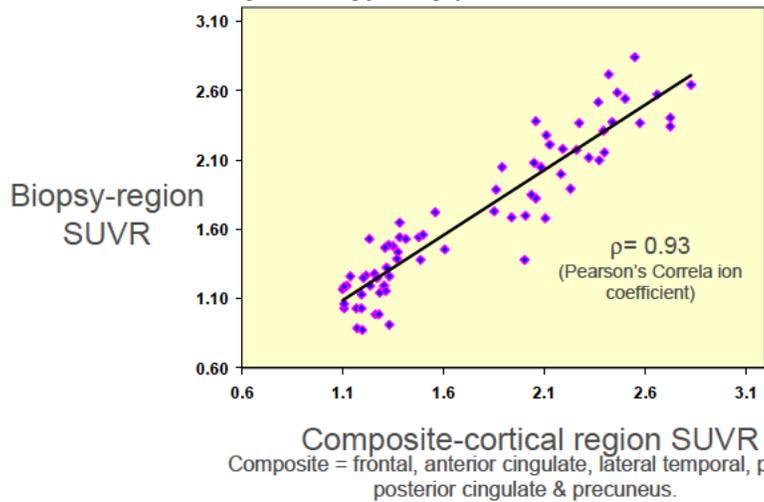
<sup>4</sup>  
Meeting with FDA  
7<sup>th</sup> September



\* Reproduced from Leinonen et.al. [ARCH NEUROL/VOL 65 (NO. 10) 2008] & Annotated with correlation.

## GE Study ALZ201 (n=72)

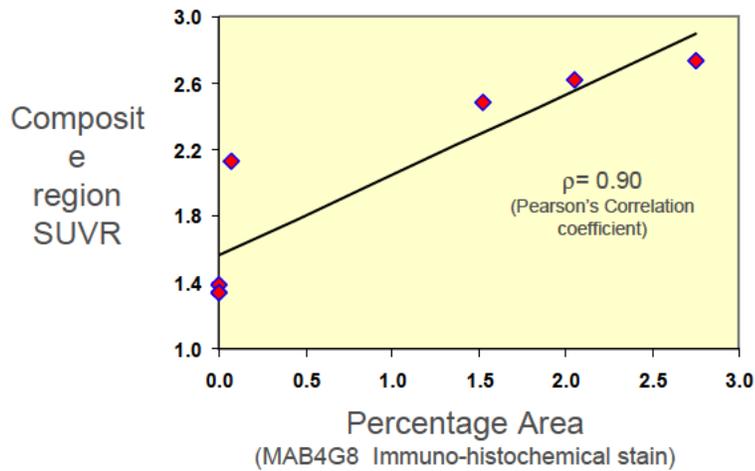
Frontal **virtual** BIOPSY region [<sup>18</sup>F]flutemetamol signal is representative of signal from composite cortical regions of the brain where amyloid is typically present in Alzheimer's disease



6  
Meeting with FDA  
7<sup>th</sup> September

## Study GE-067-008 (n=7)

Comparison of tissue based amyloid measurement with [<sup>18</sup>F]flutemetamol *in vivo* PET-based measure



**Biopsy can be reliably extrapolated to a global assessment of cerebral amyloid load**

1. Frontal Biopsy Pathology vs Frontal SUVR (Leinonen et al)
2. Frontal SUVR vs Global SUVR (ALZ201)
3. Frontal Biopsy Pathology vs Global SUVR (GE-067-008)
4. Frontal Biopsy Pathology vs Global Pathology: To be addressed (GE-067-007)

## Risk/Benefit of Biopsy Compared to Autopsy

### Biopsy

- Benefits:
  - clinically relevant patient population
  - *in vivo* tissue acquisition with immediate preservation
  - interval between scan and tissue acquisition a few days
- Risks:
  - Low probability of false positive scans: missed amyloid – prejudice against our analysis

### Autopsy

- Benefits:
  - global assessment
- Risks:
  - Terminally ill patient data dubious relevance to clinical practice
  - Results may be compromised due to post-mortem artifacts

<sup>9</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Revised Proposal for Registration (I)

### Integrated analysis to support registration

- Biopsy Studies
  - 009/011
  - 010
- Healthy young adult study

### Primary endpoint for integrated analysis now visual inspection

<sup>10</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Revised Proposal for Registration (II)

**New Study:** Healthy young adults (<40yrs)  
scanned with [<sup>18</sup>F]flutemetamol (n=30)

Primary Endpoint: visual read

FDA: Assume without histology confirmation  
healthy young adults (ApoE4 negative)  
under 40 years old are amyloid free

<sup>11</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Revised Proposal for Registration (III)

### Primary Visual Inspection Analysis

Sensitivity and Specificity of visual read  
performance will be based upon the pooled  
results (n=70) from

- Biopsy study (009/011) (n=30)
- Healthy Young Adult Study (n=30)
- Retrospective biopsy study (010) (n =10)

<sup>12</sup>  
Meeting with FDA  
7<sup>th</sup> September

## Autopsy Study

First objective (primary endpoint): define concordance between PET signal and amyloid pathology, regionally and globally

- Increase n from 3 brains to 6 brains to enable reliable estimate of between subject variation in a mixed model analysis
  - Up to 26 comparisons brain yielding up to 150 paired data points
  - Supporting hypothesis that flutemetamol signal is consistently proportional to amyloid load

Second objective (new): define relationship between biopsy area and other regions of the brain relevant to diagnosis of Alzheimer's disease

- **Pathology:** quantify numeric relationship of frontal cortical biopsy amyloid to regional and global amyloid load
- **Imaging:** quantify numeric relationship of frontal cortical biopsy SUVR to regional and global SUVR
  - Confirming that biopsy provides data that is representative of regional and global assessments

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Meeting with FDA  
7<sup>th</sup> September

## Incorporating FDA Guidance

- biopsy acceptable: reliable extrapolation to global assessment of cerebral amyloid load
- biopsy visual assessment now primary endpoint to support label
- plan bolstered with healthy young adult study to support specificity of the agent
- autopsy data will not be pooled with biopsy data
- biopsy data and healthy young adult data will be pooled
- sample size of autopsy study increased to 6 brains to provide supportive data for use of biopsy
- visual assessment methodology described

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Meeting with FDA  
7<sup>th</sup> September

## Revised Proposal for Registration (II)

**New Study:** Healthy young adults (<40yrs)  
scanned with [<sup>18</sup>F]flutemetamol (n=30)

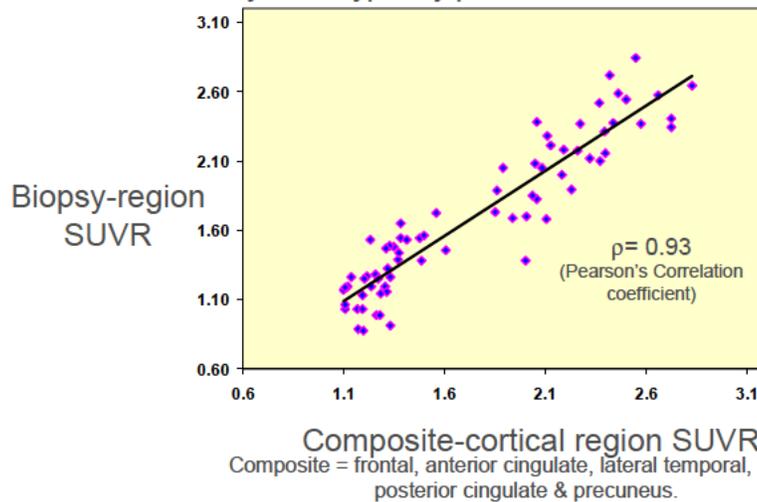
Primary Endpoint: visual read

FDA: Assume without histology confirmation  
healthy young adults (ApoE4 negative)  
under 40 years old are amyloid free

11  
Meeting with FDA  
7<sup>th</sup> September

### GE Study ALZ201 (n=72)

Frontal **virtual** BIOPSY region [<sup>18</sup>F]flutemetamol signal is representative of signal from composite cortical regions of the brain where amyloid is typically present in Alzheimer's disease

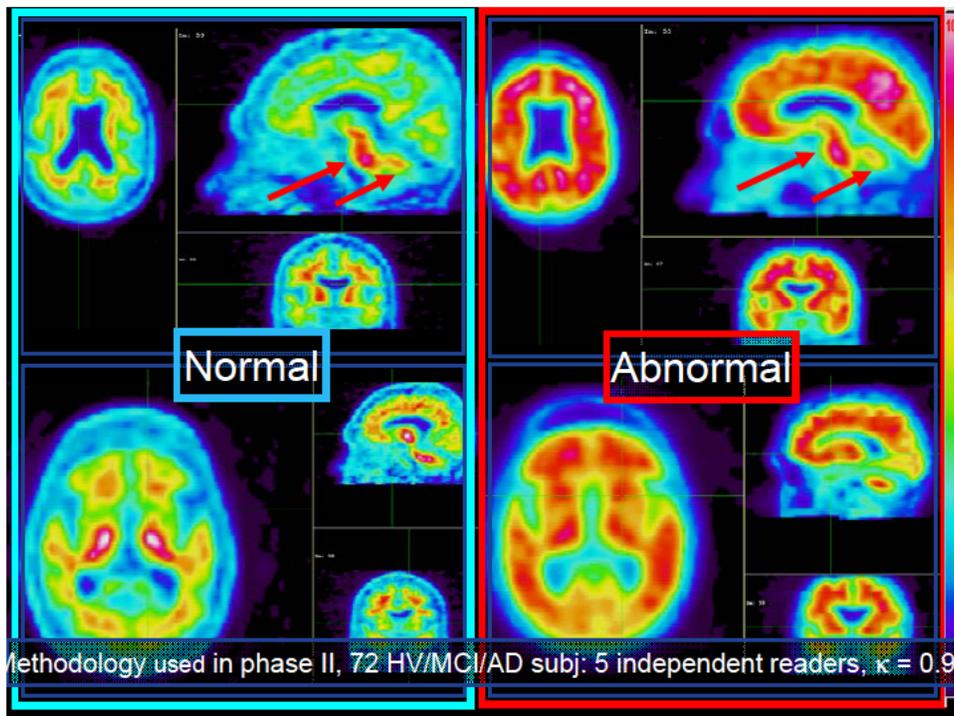


8  
Meeting with FDA  
7<sup>th</sup> September

### Basic Image Review Methodology for visual detection of A $\beta$

1. Navigation to longitudinal fissure for **sagittal** review
2. MPR crosshair mid ventricle
  - ❖ Reference **REGION** visible – cerebellum (blue/green)
  - ❖ Assess frontal/anterior cingulate, posterior cingulate/precuneus & occipital
  - ❖ Cortical tracer uptake compared to cerebellum
    - ❖ blue/green = **NORMAL**
    - ❖ Yellow/red/pink = **ABNORMAL**
3. Repeat in other hemisphere
4. Continue with a superior to inferior axial review
  - ❖ Assess frontal, parietal, precuneus, cinguli, lateral temporal, occipital, inferior frontal & striatum
5. An abnormal finding in any of these regions provides a result of **ABNORMAL**

*Methodology based on phase I data, ratified in phase II*



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/s/

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SHARON P THOMAS  
10/06/2010

# **MID-CYCLE COMMUNICATION DOCUMENTS**



NDA 203137

## LATE-CYCLE MEETING MINUTES

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on Tuesday, July 23, 2013. The purpose of the meeting was to provide you an update on the status of the review of your application.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** July 23, 2013 (3:00 pm- 4:30 pm) Face-to-Face  
**Meeting Location:** White Oak, Bldg. 22, Conf. Room 1419

**Application Number:** NDA 203137  
**Product Name:** VizamyI™ (Flutemetamol F 18 Injection)  
**Indication:** PET imaging for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment.  
**Sponsor/Applicant Name:** GE Healthcare Inc. (GEHC)

**Meeting Chair:** Libero Marzella, MD, PhD, Director (acting)  
**Meeting Recorder:** Sharon Thomas, BSc., Sr. Regulatory Health Project Manager

**FDA ATTENDEES**

Sandra Kweder, MD, Director (acting), Office of Drug Evaluation IV (ODEIV)  
Shaw Chen, MD, PhD, Deputy Director, ODE IV  
Libero Marzella, MD, PhD, Director (acting), Division of Medical Imaging Products (DMIP)  
Alex Gorovets, MD, Clinical Team Leader, DMIP  
Jagjit Grewal, Acting ADRA, ODE IV  
Phillip Davis, MD, Primary Reviewer, DMIP  
Eldon Leutzinger, PhD, CMC Team Leader, ONDQA  
Danae Christodoulou, CMC Supervisor, ONDQA  
Robert Mello, PhD, Microbiologist, OPS/NDMS  
Jyoti Zalkikar, PhD, Statistical Team Leader, OB/DBV  
Lan Huang, PhD, Statistical Reviewer, OB/DBV  
Sally Hargus, PhD, Pharm/Tox Reviewer, DMIP  
Gene Williams, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCP5  
Christy John, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCP5  
Ira Krefting, MD, Safety Deputy Director, DMIP  
CDR Sandra Rimmel, OSE Regulatory Project Manager  
Kevin Wright, Pharm D, DMEPA reviewer  
Michael Kieffer, Reviewer, OSE – Pharmacovigilance  
Peter Diak, Team Leader, OSE – Pharmacovigilance  
Adora Ndu, PhD, Reviewer- OPDP  
Joyce Weaver, PharmD, DRISK reviewer  
Don Henry, Ph.D., Compliance/OMPQ/DGMPA  
Sharon Thomas, BSc, Sr., Regulatory Project Manager, DMIP

(b) (4)

## **APPLICANT ATTENDEES**

Shamsul Alam, PhD, Head of Biometrics  
Liz Bloss, Development Strategy Lead, Regulatory Affairs  
Christopher Buckley, PhD, Imaging Technology Leader  
Paula Clark, RAC, Global Regulatory Lead, Flutemetamol  
Gillian Farrar, PhD, Senior Program Director  
Dan Frenia, Director, Quality Affairs  
Raj Long, Global Head Regulatory Affairs  
Fred Longenecker, Director, Regulatory Affairs  
Bimal Patel, Regulatory Affairs, CMC Advisor  
Paul Sherwin, MD, PhD, Senior Medical Director  
Adrian Smith, MS, Histopathologist  
Michelle Zanette, Senior Statistician

## **1.0 BACKGROUND**

NDA 203137 was dated and submitted on October 26, 2012, for drug product Vizamyl (Flutemetamol F 18 injection).

Proposed Indication: Vizamyl is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate  $\beta$  amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline. A negative Vizamyl scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Vizamyl scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions, as well as older people with normal cognition. Vizamyl is an adjunct to other diagnostic evaluations.

### Limitations of Use

- A positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder
- Safety and effectiveness of Vizamyl have not been established for:
  - Predicting development of dementia or other neurological condition
  - Monitoring responses to therapies

PDUFA Goal Date: October 26, 2013

FDA issued the LCM Background Package in preparation for this face-to face on July 16, 2013.

## 2.0 DISCUSSION

On July 16, 2013, FDA sent GEHC a Late-Cycle Meeting (LCM) package to discuss substantive review issues identified to date and objectives for the remainder of the review. On July 18, 2013, GEHC submitted an email providing responses to FDA's comments. For the purposes of the minutes, the FDA's items are in regular font, GEHC email in italics and the meeting discussion points are indicated in ***bold italics*** below.

### LCM AGENDA

Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the Meeting

#### 1. Discipline Review Letters

In addition to the contents of this background document, please also refer to the following Discipline Review (DR) letters already provided to you:

Chemistry, Manufacturing, and Controls (CMC) – July 1, 2013

*GEHC's Response to Comment #1 (e-mail dated July 18, 2013):*

*GE Healthcare has provided responses to the July 1 Discipline Review Letter, via email, on July 9. In our response, GE Healthcare agreed to the requested CMC commitments, as well as provided the draft shield and vial labels with the revisions FDA requested. Based on this submission we believe that we have addressed all current FDA CMC requests. Do you anticipate that there will be any further questions/comments on the responses we provided?*

***Discussion:***

***FDA confirmed that the sponsor had addressed all CMC information requests.***

#### 2. Information Request – 15 minutes

- We reference tables 6 and 8 in the prescribing information, we are unable to verify:
  - The sensitivity and specificity data in table 6;
  - The data for pAD in the 4<sup>th</sup> row of table 8.

*GEHC's Response to Comment #2 (e-mail dated July 18, 2013):*

*Could you please clarify the wording “..unable to verify”? Does this refer to hyperlinking and being unable to verify the derived from NDA Module 5? Or is the Statistical Review Team deriving different numbers based upon their computations?*

**Discussion:**

***FDA noted that in tables 6, 7 and 8 in section 14 of the prescribing information, the sponsor did not include data “without” anatomic images and discussed the discrepancies with the sample size in table 8. The sponsor noted that Tables 6 and 8 were updated for consistency of data without anatomic images. The sponsor explained the discrepancy in table 8.***

3. Major labeling issues – 55 minutes

- We reference section 2.6 Radiation Dosimetry which contains the adult effective dose of radioactivity from Vizamyl administration. Please note that the effective dose needs to include the radiation absorbed dose contributed by a CT scan that may be performed for the purpose of attenuation correction or reconstruction.
- We reference section 14, Clinical Studies which contains Vizamyl performance characteristics based on:
  - PET imaging with the use of anatomic correlation (CT and/or MRI);
  - The majority read results.

These results are derived from secondary analyses and do not provide meaningful additional information that warrants inclusion in the label.

**GEHC’s Response to Comment #3 (e-mail dated July 18, 2013):**

***In reviewing the labeling revisions proposed by FDA in its communication of June 28 we noted that the Agency had revised part of Table 7 (Vizamyl Scan Interpretations by Reader Training Method among Autopsied Patients) to include results for readers 1 through 5 (Study 1) based on their use of both PET and CT images to interpret the PET image. We understood this to mean that the Division considered these results to be more meaningful for clinicians, especially as more and more, PET imaging is being paired with anatomic (CT or MR) images. The value of such images is highlighted by text that FDA and GE have included in section 2.5 (Image Orientation and Display) that “If the patient’s MRI or CT brain images are available the interpreter should examine the CT or MRI images to clarify the relationship between PET Vizamyl uptake and grey matter anatomy.” For this reason we revised the rest of Table 7 to include results for readers 6 through 10 (Study 2) based on their use of both PET and CT images to interpret the PET image.***

***For consistency with the above changes to Table 7 we also revised the results in Table 6 (Vizamyl Scan Results by Reader Training Method among Patients with Autopsy) to include results for readers from Studies 1 and 2 based on their use of both PET and CT images to interpret the PET image.***

(b) (4)

(b) (4)

**Discussion:**

*FDA conveyed the need to include the estimated effective dose contributed by CT in section 2.6 of the label. FDA agreed to provide some language informing users of the estimated total effective dose by an attenuation correction and/or diagnostic CT, including a range of reference.*

*FDA agreed with the sponsor's proposed language in section 2.5 recommending readers examine CT/MRI images to better understand the relationship of Vizamyl uptake and gray matter anatomy.*

(b) (4)

4. Review Plans – 5 minutes
  - Develop Final Labeling
  - Hold Wrap-Up Meeting
  - Conduct CDTL Review
  - Conduct Division/Office Director Reviews

**Discussion:**

*See Discussion point below.*

5. Wrap up and Action Items – 10 minutes

**Discussion:**

*FDA stated that the next steps in the review were to finalize labeling and hold an internal Wrap-Up meeting. FDA noted that the application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.*

**Additional Question (GEHC)**

6. *During our conversation on June 12 you indicated that an FDA Compliance Officer had agreed to attend the July 23 meeting to discuss the PAIs at the (b)(4) and (b)(4) facilities. We note that the FDA agenda does not include a discussion of this important subject with the FDA Compliance Officer. Dan Frenia, Director of QA from GE Healthcare, will be attending the meeting to discuss the status of the PAIs. Will the Compliance Officer be attending Tuesday's meeting to discuss this important topic?*

**Discussion:**

*FDA stated specific information related to the inspectional findings is confidential, but it is currently under review and the contract manufacturers should continue to update the district offices on the progress of corrective actions following the most recent pre-approval inspections. FDA noted that the final recommendation on the acceptability of the contract manufacturing facilities will be made by the Office of Compliance on or before the PDUFA goal date.*

**3.0 OTHER SUBSTANTIVE REVIEW ISSUES**

- **Advisory Committee Meeting**  
An Advisory Committee meeting is not planned.
- **Rems or Other Risk Management Actions**  
No issues related to risk management have been identified to date.
- **Postmarketing Requirements/Postmarketing Commitments**  
There are no Post Marketing Requirements or Post Marketing Commitments under consideration at this time.

**4.0 ACTION ITEMS**

- FDA and GEHC- To finalize labeling.

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/s/  
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LIBERO L MARZELLA  
08/05/2013



NDA 203137

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

GE Healthcare Inc.  
Attention: Kevin D. White, MBA, RAC  
Senior Director and  
Americas Head, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Mr. White:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vizamyl™ (Flutemetamol F 18 Injection) 150 MBq/ML per multidose vial.

We also refer to the Late-Cycle meeting (LCM) meeting scheduled for July 23, 2013. Attached is our background package, including our agenda for this meeting.

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

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** Tuesday, July 23, 2013; 3:00 pm - 4:30 pm  
**Meeting Location:** White Oak, Building 22, Room 1421

**Application Number:** NDA 203137  
**Product Name:** Vizamyl™ (Flutemetamol F 18 Injection)  
**Indication:** PET imaging for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment.  
**Sponsor/Applicant Name:** GE Healthcare Inc.

### INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

In addition to the contents of this background document, please also refer to the following Discipline Review (DR) letters already provided to you:

- Chemistry, Manufacturing, and Controls (CMC) – July 1, 2013

#### 2. Substantive Review Issues

No substantive review issues have been identified to date.

## **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## **LCM AGENDA**

### **1. Introductory Comments – 5 minutes (RPM/CDTL)**

Welcome, Introductions, Ground rules, Objectives of the Meeting

### **2. Information Request – 15 minutes**

- We reference tables 6 and 8 in the prescribing information, we are unable to verify:
  - The sensitivity and specificity data in table 6;
  - The data for pAD in the 4<sup>th</sup> row of table 8.

### **3. Major labeling issues – 55 minutes**

- We reference section 2.6 Radiation Dosimetry which contains the adult effective dose of radioactivity from Vizamyl administration. Please note that the effective dose needs to include the radiation absorbed dose contributed by a CT scan that may be performed for the purpose of attenuation correction or reconstruction.
- We reference section 14, Clinical Studies which contains Vizamyl performance characteristics based on:
  - PET imaging with the use of anatomic correlation (CT and/or MRI);
  - The majority read results.

These results are derived from secondary analyses and do not provide meaningful additional information that warrants inclusion in the label.

### **4. Review Plans – 5 minutes**

- Develop Final Labeling
- Hold Wrap-Up Meeting
- Conduct CDTL, Division/Office Director Reviews

### **5. Wrap up and Action Items – 10 minutes**

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/s/  
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LIBERO L MARZELLA  
07/16/2013



NDA 203137

**MID-CYCLE COMMUNICATION**

GE Healthcare Inc.  
Attention: Paula Clark  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Clark:

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

We also refer to the teleconference between representatives of your firm and the FDA on Tuesday, April 2, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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

Enclosure:  
Mid-Cycle Communication

## MID-CYCLE COMMUNICATION

**Meeting Date and Time:** April 2, 2013, 11:00 am

**Application Number:** NDA 203137

**Product Name:** VizamyI™ (Flutemetarnol F 18 Injection).

**Indication:** Radiopharmaceutical diagnostic agent developed for use with positron emission tomography (PET) imaging for the visual detection of fibrillar amyloid in the form of neuritic plaques in the brain.

**Applicant Name:** GE Healthcare, Inc. (GEHC)

### FDA ATTENDEES

Shaw Chen, MD, PhD, Deputy Director, Office of Drug Evaluation IV (ODEIV)

Rafel Rieves, MD, Director, Division of Medical Imaging Products (DMIP)

Libero Marzella, MD, Deputy, Division Director, DMIP

Alex Gorovets, MD, Clinical Team Leader, DMIP

Lucie Yang, MD, PhD, Primary Medical Team Leader, DMIP

Phillip Davis, MD, Primary Reviewer, DMIP

Eldon Leutzinger, PhD, CMC Team Leader, ONDQA

Ravindra Kasliwal, PhD, CMC Reviewer, ONDQA

Robert Mello, PhD, Microbiologist, OPS/NDMS

Jyoti Zalkikar, PhD, Statistical Team Leader, DMIP

Lan Huang, PhD, Statistical Reviewer, DMIP

Sally Hargus, PhD, Pharm/Tox Reviewer, DMIP

Gene Williams, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCP5

Christy John, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCP5

Ira Krefting, MD, Safety Deputy Director, DMIP

CDR Sandra Rimmel, OSE Regulatory Project Manager

Kevin Wright, Pharm D, DMEPA reviewer

Joyce Weaver, PharmD, DRISK reviewer

Alberta Davis-Warren, BSc, Sr., Regulatory Project Manager, DMIP

### APPLICANT ATTENDEES

Shamsul Alam, PhD, Head of Biometrics

Liz Bloss, DVM, Development Strategy Lead, Regulatory Affairs

Christopher Buckley, PhD, Imaging Technology Leader

Paula Clark, RAC, Senior Manager, Regulatory Affairs

Gillian Farrar, PhD, Senior Program Director

Eric Horn, PhD, Flutemetamol Manufacturing Specialist

Gro Johansen, Manager, Analytical Development

Paul Jones, PhD, Senior Scientist, R&D

Adam King, PhD, CMC Director, Regulatory Affairs

Raj Long, Global Leader, Regulatory Affairs  
Francois Nicolas, PhD, Director of Neurology  
Bimal Patel, Regulatory Affairs, CMC Advisor  
Paul Sherwin, MD, PhD, Senior Medical Director  
Michelle Zanette, MS, Senior Statistician

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

On March 22, 2013, FDA sent an Information Request containing Chemistry and Statistical comments for GEHC to address during the meeting. For the purposes of the minutes, the FDA's comments are in regular font and the discussion points are indicated in ***bold italics*** below.

### CMC

1. Your proposed specifications for Flutemetamol F18 Injection drug product control the "total Content of Flutemetamol and related impurities" together. You need to quantify flutemetamol content separately from the related impurities content. The flutemetamol content will need to be specified in the labeling and needs to be supported by specification. Provide revised specifications for Flutemetamol F18 injection that include separate specifications for flutemetamol and for related impurities. Provide justifications for the proposed acceptance criteria for these as well as updated analytical procedure(s).

#### ***Discussion Point:***

GE asked for FDA to clarify the rationale for requesting separate specifications for flutemetamol and for related impurities. FDA stated that the Prescribing Information needs to specify the maximum amount of flutemetamol, and the requested information is needed to support the statements to be made in the label. FDA stated that the sponsor's responses will be reviewed and discussed internally.

The sponsor explained that they were unable to find a single HPLC analytical method that can accurately quantify radioactive purity and resolve flutemetamol from the impurity (b) (4) though they would still be able to meet the specification of flutemetamol plus impurity (b) (4) or less.

FDA asked about safety and efficacy data regarding the impurity. The sponsor stated that study 069 addressed safety and that the highest dose that was administered had no effect. Regarding efficacy, the sponsor stated that the pharmacokinetic summary in study 067-075 suggests that the impurity had no impact on the distribution of flutemetamol. The sponsor also stated that the impurity was present in all batches used during the Phase 3 trials.

FDA requested that the sponsor revisit previous batches, determine the total amounts of flutemetamol and co-eluting impurity, and provide this information in table format.

2. [REDACTED] (b) (4)

**Discussion Point:**

FDA is reviewing the sponsor's response.

3. Your specifications for [REDACTED] (b) (4) do not include specification for [REDACTED] (b) (4) content (impurity). Include specification for [REDACTED] (b) (4) content as part of your company's specification for [REDACTED] (b) (4). Provide updated specifications for [REDACTED] (b) (4).

**Discussion Point:**

FDA is reviewing the sponsor's response.

4. [REDACTED] (b) (4)

**Discussion Point:**

FDA is reviewing the sponsor's response.

**STATISTICAL**

5. The current efficacy data for Study 021 only includes some dummy grouping variables (such as studygr1, studygr2, ...studyg12). Please provide a sas data set that includes the unique subject identification number (usubjid) and clinical diagnosis for all the 276 subjects in study 021.

- a. The clinical diagnosis should be one variable with values such as normal, AD, MCI, ...etc. This will be necessary for subgroup analyses by clinical diagnosis.
- b. Please provide the clinical diagnosis information for the subjects with a standard of truth (autopsy and biopsy) in the same sas data set.

**Discussion Point:**

FDA is reviewing the sponsor's response. GE stated that the supplied dataset contains the 276 subjects in study 021.

**3.0 INFORMATION REQUESTS**

There were no specific information requests conveyed during this meeting.

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

The FDA stated that there have been no safety concerns identified in this phase of the review.

**5.0 ADVISORY COMMITTEE MEETING**

FDA stated that there are no plans for an Advisory Committee meeting to review the application.

**6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

The FDA informed GEHC that the proposed Late-cycle Meeting was scheduled for Tuesday, July 23, 2013, 3:00 PM, EST.

**ADDITIONAL DISCUSSION:**

FDA informed the sponsor that a revised draft label would likely be sent to GE within the next several weeks. At this time, FDA has not identified additional significant issues though the NDA review is ongoing. Additional information requests may be forthcoming. FDA is internally discussing the need for postmarketing commitments and requirements. The late cycle meeting is tentatively scheduled in late July 2013.

Regarding the information request issued March 15, 2013 and the sponsor's response received via email on March 21, 2013, FDA asked for clarification on the interpretation status of the 232 images from study 005 that were read in study 015. The sponsor stated that the final interpretations for the study 005 images are not available yet given that study 005 is an outcome study and the last subject follow-up is planned for December 2013 or January 2014.

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/s/  
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RAFEL D RIEVES  
04/24/2013

## **TEAM/ MID-CYCLE PRACTICE MEETING MINUTES**

**February 19, 2013**

**NDA 203137**

**Vizamyl (Flutemetamol F 18 Injection)**

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**Submission Date:** October 26, 2012

**PDUFA Date:** October 26, 2013

**Proposed Indication:** PET imaging for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment.

**Meeting Purpose:** To discuss review discipline specific updates and to prepare for the upcoming mid-cycle meeting.

**Meeting Attendees:** Rafel Rieves, Louis Marzella, Alex Gorovets, Lucie Yang, Phillip Davis, Eldon Leutzinger, Ravindra Kasliwal, Sally Hargus, Jyoti Zalkikar, Lan Huang, Kevin Wright, Gene Williams, Christy John, Joyce Weaver

### **1. Review Discipline Updates**

Clinical -Under review , no updates.

Nonclinical-The review is on-going.

Statistics-Under review, no updates.

Microbiology- The microbiology review is in progress and that there are no significant review issues to report at this time.

Clinical Pharmacology- The review is on-going.

CMC - Quality Amendment received from GE on 2/11/13 removing the (b) (4) site from the list of manufacturers. GE formally responded to the Information Requests submitted on 12/4/12 for CMC and Micro.

OSE/Safety- FDA informed GE that Vizamyl is conditionally acceptable. FDA conveyed Proprietary Granted letter on 2/14/13.

OSI- 3 inspections done and all ok (grove center, sponsor, acrim), 2 inspections not yet done but on track ((b) (4)).

### **2. Upcoming Mid-Cycle Meeting- Draft Presentations:**

- Clinical- Proposed indication appears reasonable, clinical utility of amyloid detection acceptable, efficacy studies met “win” criteria, application appears favorable for sponsor from clinical perspective.
- Statistical- Will continue to review 0000 original submission and upcoming 0002 ISS report. Sponsor does not evaluate reader agreement for personal trained reader study.
- Non-Clinical= Review is in progress, all study reports reviewed, PT will consult with CMC, ClinPharm, and Clinical Reviewers. (Memos in preparation), final review is on schedule to meet PDUFA V deadline, anticipate “Approval” recommendation.

### 3. Milestones/Upcoming Meetings:

MILESTONES	MILESTONE DEADLINES	MEETINGS
Receipt Date	October 26, 2012	
Day 45	December 10, 2012	Filing/Planning Meeting Dec. 3
Day 60 (Filing Date)	December 24, 2012	
Day 74 Letter Due	January 8, 2013	
Team Meeting		Jan. 24, 2013 [Thurs.]
Team /Mid-Cycle Practice #1		Feb 19, 2013 [Tues.]
Team /Mid-Cycle Practice #2		March 7, 2013 [Thurs.]
Month 5- Mid-cycle	March 25, 2013	Mid-cycle Meeting <b>March 19</b>
Mid-cycle –Communication Mtg	April 9, 2013	Mid-cycle Communication Mtg <b>April 2</b>
Labeling Meetings		<b>Apr. 9, 2013 [Tues.]</b>
		<b>April 23, 2013 [Tues.]</b>
		<b>May 7, 2013 [Tues.]</b>
		<b>May 21, 2013 [Tues.]</b>
		<b>June 6, 2013 [Thurs.]</b>
Send Labeling to GE	July 8, 2013	
Late Cycle Pre-Meeting	July 14, 2013	Late Cycle Pre-Meeting <b>July 9, 2013</b>
Send Briefing Packages to GE	July 17, 2013	By July 12, 2013[Fri.]
Issue DR Letters	July 21, 2013[Fri.]	
Late Cycle Tcon with GE	July 28, 2013	Late Cycle SponTcon <b>July 23, 2013</b>
Wrap Up Meeting	Sept. 7, 2013	Sept. 3, 2013 [Tues.]
OSI Clinical Inspection Summary Review	July 20, 2013	
Facility Inspections	(b) (4)	
<b>OSE Review</b>	<b>Jun. 28, 2013 [Fri.]</b>	
Primary Review due to TL	Jun. 28, 2013 [Fri.]	
Secondary Review due to CDTL	July. 5, 2013	

	[Fri.]	
DRISK Review/Memo	July 8, 2013 [Wed.]	
CDTL Review due to DD	Sept 20, 2013 [Fri.]	
Division Director Review	Oct. 4, 2013 [Fri.]	
Month 12 Goal Date Standard, Office Sign-off	Oct. 25, 2013 [Fri.]	

4. **DISCUSSION DURING MEETING:** No discussion during the meeting occurred regarding the timelines noted above.

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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  
02/19/2013