

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201277Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 201-277

SUPPL #

HFD # 160

Trade Name Gadavist

Generic Name Gadobutrol

Applicant Name Bayer Healthcare

Approval Date, If Known March 14, 2011

### 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

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:



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:

=====  
Name of person completing form: James Moore  
Title: Regulatory Health Project Manager  
Date: February 21, 2011

Name of Office/Division Director signing form: Shaw Chen  
Title: Deputy Office Director, ODEIV

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

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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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JAMES W MOORE  
03/30/2011

SHAW T CHEN  
03/30/2011



Bayer HealthCare Pharmaceuticals hereby certifies under FD&C Act, Section 306(k)(1) 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 New Drug Application 201,277.

Date: 3/23/10

Signature: 

John Talian, PhD

Vice President, Global Regulatory Affairs

Head of US Regulatory Affairs

Bayer HealthCare Pharmaceuticals

**\*CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS**

**TO: Mr. Philip Johnson, M.B.A. – Deputy Director, Regulatory Affairs**  
**Bayer**  
**Office: (973) 487-2181**  
**Email: [philip.johnson@bayer.com](mailto:philip.johnson@bayer.com)**

**Regarding NDA 201277: Gadovist, your email correspondence of March 10, 2011, the FDA has the following CLINICAL Information Request – March 11, 2011.**

**By 12:00 pm, EST, today, Friday – March 11, 2011, in the interest of time, first provide a response by email to the FDA and then follow-up as a formal submission to the FDA as an electronic submission via Gateway / Global Submit Review, as with all submissions to the FDA CDER – Division of Medical Imaging Products.**

**FDA CLINICAL INFORMATION REQUEST**

1. Your proposed milestone dates for the non-clinical study and for the 0-23 month human study are acceptable.
2. Your labeling changes in Sections 6, 11, and 12.3, are acceptable.

In Section 14, we request one change to both labelings (package inserts): Replace the word **(b) (4)** (see bolded) with the word “or” in the following sentence:

The categorical improvement of ( $\leq 0$ ) represents higher ( $< 0$ ) **(b) (4)** identical ( $= 0$ ) scores for the pre-contrast read, the categories with scores  $> 0$  represent the magnitude of improvement seen for the paired read.

**Revise the labelings as directed and email both labelings (annotated and clean versions in MS Word Doc) back to the FDA by 12:00 pm, EST, - today, Friday, March 11, 2011.**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THUY M NGUYEN  
03/11/2011

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 201, 277 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Gadavist Established/Proper Name: Gadobutrol Dosage Form: Injection		Applicant: Bayer Healthcare Agent for Applicant (if applicable):
RPM: James Moore		Division: HFD-160
<p><b>NDA:</b> 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>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> 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>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>March 14, 2011</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
<b>❖</b> 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 _____		<input type="checkbox"/> Received

<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.

❖ Application Characteristics <sup>2</sup>	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  <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  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  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request  Comments:  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  REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required	
❖ 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)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other FDA Press Release

<sup>2</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.

<p>❖ Exclusivity</p>	
<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 BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA #      and date 10-year limitation expires:
<p>❖ Patent Information (NDAs only)</p>	
<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>3</sup>	x
<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) AP March 14, 2011
<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>	x
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	x
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/25/10

❖ 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> )	<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>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
❖ 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> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	x
❖ 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> </ul>	x, March 4, 2011, August 13, 2010 x, August 11, 2010, February 28, 2011
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM ,March 30, 2011 <input checked="" type="checkbox"/> DMEPA ,March 3, 2011 <input checked="" type="checkbox"/> DRISK ,March 31, 2011 <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews Maternal Health, February 3, 2011
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) ( <i>indicate date of each review</i> )	March 8, 2011, February 3, 2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ 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>	
<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
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>March 9, 2011</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	x

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	x
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg February 4, 2010
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg August 28, 2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	January 21, 2011
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	x
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 11, 2011
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 27, 2011
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 16, 2011
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 2
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	January 27, 2011
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See Medical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input type="checkbox"/> None x- See DRISK Review March 31, 2011
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested x

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

Version: 8/25/10

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<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	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None February 24, 2011
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None February 25, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None February 25, 2011
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None February 15, 2011
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None February 15, 2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 14, 2011
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None February 25, 2011
❖ Microbiology Reviews	<input type="checkbox"/> Not needed January 13, 2011
<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 (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ 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 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 Chemistry Review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	See Chemistry Review
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	See Chemistry Review
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>6</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.

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/s/  
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JAMES W MOORE  
04/04/2011

**\*CONFIDENTIAL**

## **FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)**

### **TELECONFERENCE (TCON) MINUTES**

**NDA:** 201277  
**DRUG NAME:** Gadavist  
**SPONSOR:** Bayer HealthCare  
**TCON DATE:** Thursday, March 10, 2011 at 1:00 pm

#### **SPONSOR PARTICIPANTS**

Thomas Balzer, M.D., Vice President and Head, Global Clinical Development  
Christine Becker, Head, Diagnostic Imaging, Global Regulatory Affairs  
Josy Breuer, M.D., Ph.D., Global Clinical Development  
Lynn Carmichael, Associate Director, Global Regulatory Affairs  
Salvatore DeSena, M.D., M.B.A., Associate Director, US Medical Affairs  
Wolfgang Ebert, Ph.D., Global Project Management  
Harold Goldstein, M.D., Vice President, US Medical Affairs  
Daniel Haverstock, M.S., Principal Statistician, Clinical Statistics  
Birte Hofmann, D.V.M., Pharmacokineticist, Clinical Pharmacology  
Rainer Hofmeister, D.V.M., Toxicologist, Global Early Development - Toxicology  
Philip Johnson, M.B.A., Deputy Director, Global Regulatory Affairs  
Tom Lopac, Senior Labeling Manager, Packaging and Labeling Development  
Herb O'Brien, Senior Local Labeling Manager, US Regulatory Affairs  
Martin Rosenberg, M.D. Senior Director, Global Clinical Development  
Sarit Rotman, R.Ph., Pharm.D., M.B.A., Deputy Director, US Marketing  
Marta Santiuste, M.D., Ph.D., Global Clinical Development

#### **FDA PARTICIPANTS**

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Olayinka Dina, Ph.D., Pharm/Tox Reviewer  
Sandra Griffith, Pharm.D., OSE Project Manager  
Christy John, Ph.D., Clinical Pharmacology Reviewer  
Ira Krefting, M.D., Safety Team Leader  
Adebayo Lanionu, Ph.D., Pharm/Tox Team Leader  
Eldon Leutzinger, Ph.D., CMC Pharmaceutical Assessment Lead  
Cathy Miller, Pharm.D., OSE-DMEP Safety Reviewer  
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager  
David Place, Ph.D., Chemistry Reviewer  
Renee Tyson, M.S., Safety Project Manager  
Lucie Yang, M.D., Ph.D., Acting Clinical Team Leader

**NDA 201277: Gadavist**  
**Page 2**

**AGENDA: To discuss the labelings, labels and post-marking requirements as it relates to the submission dated May 14, 2010 – See EDR.**

**Labelings (Package Inserts):** As discussed, the Sponsor agreed to the labeling changes in Sections 6, 11, 12.3, and 14 and will submit revised labelings by COB, 03/10/11. Also, the Sponsor agreed to include a dosing chart to be considered as promotional material and submit it to DDMAC for review.

**Bar Codes on Labels:** The Sponsor explained that the (b) (4)  
(b) (4) The linear bar code on all packaging components contains the NDC number

**Repeat Dose Study in Neonatal Rats:** FDA recommended adding an arm-study for dosing starting at PND 4. By (b) (4), 2011, the Sponsor will provide additional explanation behind their rationale for recommending dosing starting at PND 10 (instead of PND 4).

The Sponsor will exclude any pre-term babies from our clinical study of 0 - 23 months, and exclude pre-term babies in any future label for Gadavist.

With regards to the Sponsor repeated-dose neonatal rat study plan received by email, 03/09/11, the FDA will provide feedback by April 4, 2011.

**Revised Dates for Post-Marketing Requirements:** The (b) (4)  
(b) (4) currently planned study and plan to begin dosing in mid-(b) (4). The Sponsor is will extend the study completion and final report submission dates by approximately 5 months in the event that a separate neonatal rat study needs to rescheduled or conducted. The dates for the study in children 0 - 23 months have also been extended accordingly.

**For the repeated-dose neonatal rat study:**

**Final Protocol Submission:** May (b) (4) 2011

**Study/Trial Completion** (b) (4) January (b) (4) 2012

**Final Report Submission:** June (b) (4), 2012

**For the clinical study in children 0 - 23 months:**

**Final clinical protocol submitted to FDA:** July (b) (4), 2012  
(b) (4)

**Last Patient, Last Visit (Study Completion):** March (b) (4), 2014

**Final CSR Submission to FDA:** January (b) (4) 2015

**NDA 201277: Gadavist**  
**Page 3**

**ACTION ITEMS:**

1. The Sponsor will submit revised labelings by COB, today, 03/10/11.
2. The FDA will provide feedback by 04/06/11, re: the repeated-dose neonatal rat study plan.
3. The Sponsor will include a dosing chart as part of the promotional material and submit it to DDMAC for review.

**Minutes Recorded By:** T.Nguyen, DMIP

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/s/  
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THUY M NGUYEN  
03/14/2011



NDA 201277

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Bayer HealthCare Pharmaceuticals Inc.  
P.O. Box 1000  
Montville, New Jersey, 07045-1000

ATTENTION: Philip Johnson  
Deputy Director, Global Regulatory Affairs

Dear Mr. Johnson,

Please refer to your New Drug Application (NDA) dated May 13, 2010, received May 14, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gadobutrol Injection, 1 mmol/mL.

We also refer to your February 18, 2011, correspondence, received February 22, 2011, requesting review of your proposed proprietary name, Gadavist. We have completed our review of the proposed proprietary name, Gadavist, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 18, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, James Moore at (301) 796-2050.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
03/04/2011

February 25, 2011

Attached are FDA edits to your proposed labels. Please review these, incorporate revisions, correct format and typographical errors and justify any substantive alterations. Please respond by March 2. We will attempt to arrange a brief telephone discussion to describe our major edits/requests; we are attempting to schedule this for Monday/February 28th. Please acknowledge receipt of this request. Please call me as soon as possible and let me know your availability for a tcon on Monday. My telephone number is (301) 796-2050. Thanks so much. James.

These draft labels were sent to Bayer Healthcare today electronically.

James Moore, PharmD., M.A.  
Project Manager, DMIP

39 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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JAMES W MOORE  
02/25/2011



NDA 201277

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Bayer HealthCare Pharmaceuticals Inc.  
P.O. Box 1000  
Montville New Jersey 07045-1000

ATTENTION: Philip Johnson  
Deputy Director, Regulatory Affairs

Dear Mr. Johnson:

Please refer to your New Drug Application (NDA) dated May 13, 2010, received May 14, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gadobutrol Injection, 1 mmol/mL.

We acknowledge receipt of your February 10, 2011 correspondence, received February 10, 2011, notifying us that you are withdrawing your December 2, 2010 request for a review of the proposed proprietary name [REDACTED] (b) (4). This proposed proprietary name request for [REDACTED] (b) (4) is considered withdrawn as of February 10, 2011.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Griffith, 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 James Moore at (301) 796-2232.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
02/24/2011



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation OODP

**FACSIMILE TRANSMITTAL SHEET**

**DATE: February 14, 2011**

<b>To: Phillip Johnson</b>	<b>From:</b> James Moore
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050

**Subject:** Statistical Request, Urgent, NDA 201,277, Gadobutrol

**Total no. of pages including cover:** 2

**Comments:** These comments are draft and are subject to addition, deletion, or revision.

**Document to be mailed:** YES  NO

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February 14, 2011

Regarding your pending application NDA 201,277 for Gadovist (Gadobutrol) Injection, the reviewing statistician has an urgent request.

1. The statistical reviewer has noticed that, although the FAS for Study 310123 is 336, virtually all the tables that list FAS results have N at about 315. Explain this difference?

Send your response to this inquiry to me via email at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) , cc Dr. Anthony Mucci at [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov). You should respond to this request as soon as possible. Follow up your email response with a submission to your pending NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Regulatory Project Manager, DMIP

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/s/  
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JAMES W MOORE  
02/14/2011



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation OODP

**FACSIMILE TRANSMITTAL SHEET**

**DATE: February 8, 2011**

<b>To: Phillip Johnson</b>	<b>From:</b> James Moore
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Pharmacology Request, Pending NDA 201,277	

**Total no. of pages including cover:** 2

**Comments: These comments are draft and are subject to addition, deletion, or revision.**

**Document to be mailed:** YES  NO

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February 8, 2011

Regarding your pending NDA 201,277 for Gadobutrol, the reviewing pharmacologist has the following request.

1. Provide the location of information on Stability and Homogeneity of Dose formulations, and Certificate of Analysis for studies:

A41318

A08936

A10548

A28309

You should respond to this request via email to me at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov), cc Dr. Olayinka Dina [Olayinka.Dina@fda.hhs.gov](mailto:Olayinka.Dina@fda.hhs.gov) and cc Dr. Adebayo Lanijonu at [Adebayo.Lanijonu@fda.hhs.gov](mailto:Adebayo.Lanijonu@fda.hhs.gov). You should respond to this request by COB today, February 8, 2011. Follow-up your email response with a submission to your NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Regulatory Project Manager, DMIP

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/s/  
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JAMES W MOORE  
02/08/2011

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Time/Date:** 1530- 1600 EST 8 February 2011

**To:** Carol Holquist

**CC:** Chris Wheeler

**From:** Sandra J. Griffith

**Application:** NDA 201277, (b) (4) (Gadobutrol Injection), RCM 2010-2532.

**OSE Goal Date:** 2/28/2011

**FDA Participants: OSE**

Carol Holquist, RPh., DMEPA Director  
Zachary A. Oleszczuk, PharmD, DMEPA Team Leader  
Cathy A. Miller, MPH, BSN, DMEPA Primary Reviewer,  
Sandra J. Griffith, BSN, RN, OSE Safety Regulatory Project Manager

**FDA Participants: OND**

Rafel Rieves, M.D., Division Director  
Libero Marzella, M.D., PhD., Deputy Division Director, DMIP  
Eldon Leutzinger, PhD., Pharmaceutical Assessment Lead, Chemistry  
Barbara Stinson, D.O., Primary Clinical Reviewer  
James Moore, PharmD, Project Manager

**Sponsor/Applicant:** Bayer Health Care

Philip Johnson: US Regulatory Affairs and POC

Sarit Rotman, US Brand Team

(b) (4)

Christian Schalk, Global Trademarks  
Maria Rivas, US Medical Affairs  
Wolfgang Ebert, Global Project Management

**Background:**

A request for review of the proposed proprietary name (b) (4) was submitted to the FDA on 12/1/2010. During the initial stages of review DMIP expressed concern that the proposed name might mislead practitioners to believe the product did not contain Gadolinium and DDMAC had no objections to the name from a promotional standpoint. Although DMEPA did not identify any risks associated with look-alike or sound-alike names, DMEPA agreed with DMIP's concern and considered the name misleading. DMEPA wanted to communicate this deficiency and discuss alternate nomenclature options with the sponsor via telephone due to the upcoming PDUFA deadline for review of the overall application.

**Discussion**

DMIP/DMEPA communicated the following concerns to the Bayer Health Care representatives: Concern of (b) (4) being misinterpreted as without gadolinium. Another possible misinterpretation could be that this GBCA has 1 gadolinium ion (safer) whereas others have more than 1 gadolinium ion in each complex. DMEPA discussed other options the sponsor could consider in developing a new proposed name for the product that would not be in conflict with USAN stem policy. DMEPA discussed the option of the Applicant considering a slight variation to the original proposed name, Gadovist, which was found unacceptable due to the use of the USAN stem 'Gado-'. Since DMEPA did not find any other concerning look-alike or sound-alike names for the propose name, Gadovist, we proposed that the Applicant change

the fourth letter 'o' to another similar letter, our preliminary assessment of the name would not likely change.

**Steps Forward**

The sponsor was advised that they have the following options:

1. Wait for the official completed results of our review, which DMEPA will try to finalize on 3/2/2011.
2. Withdraw the proposed proprietary name (b) (4) and submit their secondary name, (b) (4)
3. Withdraw the proposed proprietary name (b) (4) and submit a new proprietary name for review.
4. DMEPA agreed to a cursory review of a list of proposed names prior to official submission since the application is close to the PDUFA review goal date.

**Decision:**

Sponsor POC verbalized understanding of above discussion and stated they will withdraw the proposed proprietary name (b) (4) and consider their options. They agreed to send a few proposed names for DMEPA comments before they formally submit a new proprietary name for review.

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/s/  
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SANDRA J GRIFFITH  
02/11/2011



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation OODP

**FACSIMILE TRANSMITTAL SHEET**

**DATE: December 6, 2010**

<b>To: Phillip Johnson</b>	<b>From:</b> James Moore
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050

**Subject:** Clinical Request, AVG Blinder Reader Score per dose (Gadobutrol), NDA 201,277

**Total no. of pages including cover:** 2

**Comments:** These comments are draft and are subject to addition, deletion, or revision.

**Document to be mailed:**  YES  NO

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December 6, 2010

The clinical reviewer has the following comments and request regarding pending NDA 201,277 for Gadovist.

For the Phase 2 study 308200 the average reader score (CVS) for the efficacy variables and the standard deviation are listed for each dose (0.03, 0.1, and 0.3 mmol kg bw) pre contrast and pre + post contrast. For all 3 doses, both the individual study report and the tables in the NDA, the value for the pre is identical to the pre + post which cannot be since the individual values are not the same. This information can be found in table 10 in text and table or listing 14 in the NDA.

Please clarify and provide average CVS and standard deviations pre and pre + post for the three doses for the average reader.

You should respond to this request by COB Monday, December 13, 2010. Send your response to me at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) and cc Dr. Barbara Stinson at [Barbara Stinson@fda.hhs.gov](mailto:Barbara.Stinson@fda.hhs.gov). Follow up this response with a submission to your NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Regulatory Project Manager, DMIP

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/s/  
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JAMES W MOORE  
12/07/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: December 3, 2010**

<b>To: Phillip Johnson</b>	<b>From: James Moore</b>
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number: (973) 487-2016</b>	<b>Fax number: (301) 796-9849</b>
<b>Phone number: (973) 487-2181</b>	<b>Phone number: (301) 796-2050</b>
<b>Subject: FDA Response, Meeting Package, November 22, 2010, Gadovist (Gadobutrol), NDA 201-277</b>	

**Total no. of pages including cover: 5**

**Comments: These comments are draft and are subject to addition, deletion, or revision.**

**Document to be mailed:**             YES                     NO

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December 3, 2010

Please refer to your submission of November 22, 2010 for New Drug Application (NDA) 201,277 which consists of the Briefing Document for a teleconference scheduled for Monday, December 6, 2010 from 11:00 AM – 12:00 PM. We reviewed your submission and have the following responses to your questions. FDA responses are in **BOLD**. Your questions are in *italics*.

Applicant's Question 1:

1. *We would appreciate receiving the Division's perspectives on the key NDA review issues regarding NSF in association with Gadovist. What issues has the Division identified that will impact the review of the overall NDA? What are the key issues and questions that the Division will be taking to the Advisory Committee in January 2011?*

**FDA Response to Question 1:**

**The division will likely pose a question to the Advisory Committee related to the overall risk-benefit of Gadovist. At this point, the efficacy data appear to support Bayer's general conclusions. We regard the safety of Gadovist as a major issue for the upcoming Advisory Committee, particularly the potential for increased risk of NSF. Our ongoing review highlights the following issues:**

- a. **The occurrence of NSF in the vulnerable, severe renal failure population when a higher-than-recommended Gadovist dose was administered, suggesting a narrow safe-dosing range. As discussed during the teleconference on November 23, 2010, we are particularly concerned about the potential for medication error and excessive dosing due to the double strength of Gadovist relative to other U.S. FDA-approved gadolinium-based contrast agents with a similar indication.**
- b. **The lack of an explanation for the occurrence of single agent Gadovist NSF cases in light of the level of worldwide Gadovist usage to date, given the provided physicochemical data for Gadovist suggesting minimal to no release of free gadolinium ion under certain conditions.**
- c. **The unusually long latency between Gadovist administration and onset of NSF symptoms or NSF diagnosis (Case 200828599GPV), suggesting a novel or hitherto uncharacterized mechanism of NSF initiation.**
- d. **The occurrence of NSF in a patient with an eGFR greater than 30 mL/min/1.73 m<sup>2</sup> who was administered Gadovist (Case**

**200923701GPV), again suggesting a rare or unique characteristic for Gadovist.**

Applicant's Question 2:

2. *Does the Division have any questions on Bayer's summary of NSF pertaining to Gadobutrol? Does the Division have any concerns or suggestions as it pertains to the inclusion of this summary in the Advisory Committee briefing document (to be finalized in mid-December 2010)?*

**FDA Response to Question 2:**

**Bayer's Meeting briefing document succinctly summarizes information available from a variety of sources. We have the following suggestions which may provide the Advisory Committee with a more comprehensive understanding of the risk of NSF as it pertains to Gadovist (inclusion of this information in a briefing document is at your discretion and should involve consideration of the format/privacy considerations and your determination of the added value of the information/we suggest you discuss these items in our upcoming telephone call and supply a written summary to the NDA):**

- a. **Include a discussion of the conditional stability (thermodynamic stability measured at physiologic pH) of Gadovist and comment on the risk of NSF in light of its conditional stability.**
- b. **List the readers of all biopsy slides (or the institutions at which these were read) and whether the slides have undergone an independent review.**
- c. **Clarify whether Dr. Shawn Cowper has been formally consulted to review any of the biopsy slides for the cases listed in the summary.**
- d. **Summarize and comment on the correspondences in the medical literature questioning the NSF diagnosis in some of the listed cases.**
- e. **Include a summary of your response to the chemistry/manufacturing/control information request issued December 1, 2010.**
- f. **Present any additional information concerning Gadovist and NSF, such as from the NSF registry at the** (b) (4)

Applicant's Question 3

3. *Can the Division provide any feedback on the updated labeling submitted on October 22, 2010 to address the potential for medication errors?*

**FDA Response to Question 3:**

We have the following preliminary suggestions based on an ongoing review of the draft vial label:

- a. Replace (b) (4) with "1 mmol/mL" to be consistent with the draft Prescribing Information (PI).
- b. Remove "Dose: (b) (4)" to reduce potential confusion due to too many numbers.
- c. Replace (b) (4) with a descriptor such as "WARNING" or "CAUTION" to alert health care professionals about the concentration of Gadovist.
- d. Move the alert about the concentration to the Principal Display Panel.
- e. Replace the abbreviation (b) (4) with "intravenous."
- f. Do not highlight "7.5 mL."

**Additional FDA Comments:**

4. Clarify the rationale for formulating Gadovist as a (b) (4) solution.
5. We acknowledge your December 2, 2010 submission to NDA 201,277 requesting a Proprietary Name Review. We encourage Bayer to develop a trade name for gadobutrol that would more easily differentiate your product from other gadolinium-based contrast agents.
6. We encourage Bayer to consider developing a dose chart (similar to the table in Section 2.1 in the draft PI) for easy reference by health professionals (e.g. to tape on the wall in the MRI suite). This dose chart would ideally be easily distinguishable from charts used by MRI technologists for other GBCAs.
7. Regarding the draft Prescribing Information, we recommend that Bayer replace all instances of the word "enhanced" with "contrasted."

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Regulatory Project Manager, DMIP

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/s/  
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JAMES W MOORE  
12/03/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** December 1, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Chemistry/Clinical Request NSF Cases, Gadovist (Gadobutrol) Injection, NDA 201-277	

**Total no. of pages including cover:** 3

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December 1, 2010

Regarding your pending NDA for Gadovist, NDA 201-277, the reviewing chemistry and clinical team have the following comments and information requests.

In your November 22, 2010 submission you summarized 10 cases of NSF reported in Europe for this product, though some may have been confounded and not definitively linked to administration of the product. The occurrence of NSF in patients receiving Gadovist is noteworthy since Gadovist's molecular structure and other features have been proposed as a basis for placing it in the low risk group of Gadolinium contrast agents.

Since the cluster of cases in Europe was part of your safety reporting for the product we are requesting some additional information on the product administered during this period. Specifically, we request additional information to correlate the cases with the drug's chemistry/manufacturing/control (CMC) aspects.

1. Your November submission included a concise table (page 34). We request development of a similar table that incorporates the following information for each case: the case number, NSF report date, date of GBCA exposure, dose, and product lot number (or other specific tracer information) and clinical procedure(s), e.g., MRI of head. Provide supportive text if additional information is available to help assess any CMC impact upon the NSF occurrence.
2. Was there a formulation or significant manufacturing process change prior to occurrence of these cases?
3. If there was a formulation change, what was the date of the formulation change of Gadovist in Europe?
4. If there was a formulation change, what was the nature of the formulation change? Was there a change in the concentration of the excipients, or concentration of the active ingredient before, during, or after the occurrence of the NSF cases in Europe? Were ingredients added, removed from the product during the occurrence of these NSF cases?
5. Were there specific product quality issues that could affect the stability or quality of the product during this period?
6. Please provide manufacturing information on the batches of product associated with those cases (e.g., batch records, certificates of analysis - lot numbers).

You should provide this information to me by COB Friday, December 17<sup>th</sup> at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov), cc Dr. David Place at [David.Place@fda.hhs.gov](mailto:David.Place@fda.hhs.gov), cc Dr. Eldon Leutzinger at [Eldon.Leutzinger@fda.hhs.gov](mailto:Eldon.Leutzinger@fda.hhs.gov), cc Dr. Barbara Stinson at [Barbara.Stinson@fda.hhs.gov](mailto:Barbara.Stinson@fda.hhs.gov) and Dr. Ira Krefting at [Ira.Krefting@fda.hhs.gov](mailto:Ira.Krefting@fda.hhs.gov). You should follow up the submission to me with a submission to your NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Regulatory Project Manager, DMIP

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/s/  
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JAMES W MOORE  
12/01/2010

## Record of Telephone Conversation

NDA: 201-277 (gadobutrol)

Sponsor: Bayer

Today's date: November 23, 2010

Speakers:

For FDA: James Moore, Dwaine Rieves, Lucie Yang, Young Moon Choi, Ira Krefting, Eldon Leutzinger, Bayo Laniyonu, Alex Gorovets, Olayinka Dina

For Bayer: Philip Johnson, Pam Cyrus, Hank Goldstein and several others

FDA called Bayer to provide preliminary highlights from the ongoing review of gadobutrol. FDA noted that, to date:

- efficacy data appear to support the sponsor's general conclusions

- preclinical and clinical data also appear to support the sponsor's contention that gadobutrol is similar to the "lower" risk gadolinium-based contrast agents

- the concern about medication errors appears particularly important and one perspective involves consideration of a contraindication for use of the drug among high risk patients (renal risk category) related to the risk for medication error/excessive dosing.

FDA noted that the preceding comments were preliminary and subject to change. FDA also noted that the upcoming advisory committee will likely have a question related to overall risk-benefit and perhaps consideration of medication error. FDA noted that these subjects will be discussed further in the December 6, 2010 and the company may wish to provide additional information related to medication errors to assist in that discussion.

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/s/  
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RAFEL D RIEVES  
11/23/2010



NDA 201,277

**MEETING REQUEST GRANTED**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Phillip Johnson  
Deputy Director, Global Regulatory Affairs  
P.O.Box 1000  
Montville, NJ 07045-1000

Dear Mr. Johnson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gadovist (Gadobutrol) Injection.

We also refer to your October 29, 2010, correspondence requesting a Type A Meeting to gain an understanding of the review issues the Division has identified regarding NSF in association with Gadobutrol Injection, and present the analyses that Bayer plans to include in the Advisory Committee briefing document. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The teleconference is scheduled as follows:

Date: December 6, 2010

Time: 11:00 AM - 12:00 PM

Phone Arrangements: The Applicant will provide the call in number.

CDER Participants: Rafel Rieves, M.D., Director, DMIP  
Alexander Gorovets, M.D., Clinical Team Leader, DMIP  
Barbara Stinson, D.O., Clinical Reviewer, DMIP  
Anthony Mucci, Ph.D., Statistical Reviewer, OB  
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB  
Adebayo Lanionu, Ph.D., Pharmacology/Toxicology Team Leader, DMIP  
Olayinka Dina, Ph.D., D.V.M., Pharmacology/Toxicology Reviewer, DMIP  
David Place, Ph.D., Chemistry Reviewer, ONDQA  
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP  
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, OCP  
Ira Krefting, M.D., Clinical Safety Officer, DMIP  
Rene Tyson, M.S., Safety Project Manager, DMIP  
Kyong Kang, PharmD., Chief, Project Management Staff  
James Moore, PharmD., M.A., Project Manager, DMIP

Submit background information for the meeting (one electronic copy to the application and five desk copies to me) by November 22, 2010 as stated in your November 15, 2010 e-mail correspondence. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by that date, we may cancel or reschedule the meeting.

Submit the five desk copies to the following address:

James Moore, PharmD., M.A.  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 2243  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-2050.

Sincerely,

*{See appended electronic signature page}*

James Moore, PharmD., M.A.  
Project Manager  
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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JAMES W MOORE  
11/17/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** November 17, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050

**Subject:** Chemistry Request 1, Relaxivity, Gadovist (Gadobutrol), NDA 201,277

**Total no. of pages including cover:** 2

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November 17, 2010

Regarding your pending NDA 201,277 for Gadovist the reviewing chemist has the following request.

1. Provide the relaxivity specifications and test for the gadobutrol drug substance.

You should provide this information by COB Tuesday, December 14, 2010. Send your response to me via email at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) and cc Dr. David Place at [David.Place@fda.hhs.gov](mailto:David.Place@fda.hhs.gov). Follow up your email response with a submission to your NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

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/s/  
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JAMES W MOORE  
11/17/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** November 17, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050

**Subject:** Microbiology Request, Gadovist (Gadobutrol), NDA 201,277

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November 17, 2010

Regarding your pending NDA 201,277 for Gadovist (Gadobutrol), the reviewing microbiologist has the following comments and requests.

Please provide the following information or a reference to its location in the subject submission.

1. Provide information to support container closure integrity after the maximum potential [REDACTED] (b) (4) submitted container closure studies support a [REDACTED] Your (b) (4) .
2. Provide the results of three minimum load [REDACTED] validation runs.
3. Provide a rationale for the use of X-ray contrast media as a representative product in place of Gadovist [REDACTED] (b) (4) studies.
4. Provide a description of the post-approval stability program.
5. Provide the final sterility test validation report.

You should respond to the request by COB, December 30, 2010. You should provide your response via email to me at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) and cc Dr. Jessica Cole at [Jessica.Cole@fda.hhs.gov](mailto:Jessica.Cole@fda.hhs.gov). Follow up your email response with a submission to your pending NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

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/s/  
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JAMES W MOORE  
11/17/2010



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Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** November 4, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Clinical Request 6 Clarification Number of AEs Reported, Gadovist (Gadobutrol), NDA 201,277	

**Total no. of pages including cover:** 2

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November 4, 2010

Regarding pending NDA 201,277 for Gadovist, the reviewing medical officer has the following comments and request.

1. Section 2.1.4.2 of the ISS notes 6 subjects D/C-ed study medication and 7 subjects D/C-ed the study due to AEs. It is also noted that only one subject discontinued due to drug related AEs.
2. Both Table 41 and the narratives contained in section list 9 subjects as discontinuing the study due to AEs. Table 39, Table 41, and the subject narratives list 3 subject discontinuations due to drug-related AEs.

Please clarify the reasons for D/Ced study medication and clarify the number of AEs reported in the trials.

You should respond to this request via email to me at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) by COB Monday, November 8, 2010.

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIHP

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/s/  
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JAMES W MOORE  
11/04/2010



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/s/  
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RENE C TYSON  
11/08/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: October 14, 2010**

<b>To: Phillip Johnson</b>	<b>From: James Moore</b>
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number: (973) 487-2016</b>	<b>Fax number: (301) 796-9849</b>
<b>Phone number: (973) 487-2181</b>	<b>Phone number: (301) 796-2050</b>
<b>Subject: Statistical Request2 Clarification, Gadovist (Gadobutrol), NDA 201,277</b>	

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October 14, 2010

During the review of your pending NDA 201, 277 for Gadovist, we have noted the following:

1. Study 310123 presents Mean #Lesions (Paired Gadovist) = 8.24; Mean # Lesions (Unenhanced) = 8.08
2. Study 310124 presents Mean #Lesions (Paired Gadovist) = 2.97; Mean # Lesions (Unenhanced) = 2.65

Please comment on the apparent discrepancy between these two studies in relation to the number of lesions.

Please send your response to me via e-mail at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov), cc Dr. Anthony Mucci at [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov) and cc Dr. Barbara Stinson at [Barbara.Stinson@fda.hhs.gov](mailto:Barbara.Stinson@fda.hhs.gov). Please provide a response to this request by noon on Tuesday, October 19, 2010. Follow up your email response with a submission to your NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

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/s/

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JAMES W MOORE  
10/14/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** October 14, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Clinical Request 5 Clarification, Demographics, Gadovist (Gadobutrol), NDA 201,277	

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October 14, 2010

Regarding your e-mail of October 8, 2010 in which you requested clarification of FDA's October 6, 2010 clinical request, FDA has the following response.

Reference to the location of the information is not sufficient to adequately address FDA's October 6, 2010 request. You should provide the information as requested for the two Phase 3 studies 310123 and 310124.

To reemphasize and further clarify what is needed, please note the following statement:  
A subject listing with weights and volume of gadobutrol injection administered is needed.

The timeline proposed in your email is acceptable.

Please send your response to me via e-mail at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov), and cc Dr. Barbara Stinson at [Barbara.Stinson@fda.hhs.gov](mailto:Barbara.Stinson@fda.hhs.gov). Follow up your email response with a submission to your NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

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/s/

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JAMES W MOORE  
10/14/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** October 14, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Response Microbiology Question 17, Gadovist (Gadobutrol), NDA 201,277	

**Total no. of pages including cover:**

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October 14, 2010

In response to your e-mail of October 8, 2010 below regarding NDA 201, 277, the microbiologist has the following comments. Your inquiry appears in italics before the microbiologist's response.

*In the Microbiology Request 1, faxed to Bayer on 12 August 2010, comment #17 states the following:*

*17. During the sterility test samples should be compared to the negative control and not the positive control to determine whether growth has occurred.*

*I can confirm that Bayer does compare the test samples to the negative control to determine if growth has occurred, and our complete reply to these comments will reflect this.*

***Question for the FDA reviewer:*** *Is this comment being provided to us because there is reference within our NDA to comparison to a positive control? If so, can the FDA reviewer please identify the specific section / report? Alternatively, is this comment being provided to us as guidance in case additional sterility testing is conducted?*

#### **Microbiology Reviewer Comment**

During review of NDA 201-277 the method for determining a negative sterility test was unclear. Document A45453 states on page 7/9 Section 4: (b) (4)

(b) (4) We note that this document describes the sterility test validation method. Insufficient information was present in the description of the sterility test method to assess what criterion was used to determine the results from sterility test samples. Document K217E180 page 31/35 states: (b) (4)

From a microbiological perspective, shaking the sterility test sample could potentially dislodge and suspend a small but visible cluster of microbiological growth. Samples should be visually compared to the negative control prior to shaking but may be shaken after the initial observation. All samples should be compared to the negative control to assess potential microbial contamination.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

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/s/

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JAMES W MOORE  
10/14/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: October 6, 2010**

<b>To: Phillip Johnson</b>	<b>From: James Moore</b>
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number: (973) 487-2016</b>	<b>Fax number: (301) 796-9849</b>
<b>Phone number: (973) 487-2181</b>	<b>Phone number: (301) 796-2050</b>
<b>Subject: Clinical Request 5, Demographics, Gadovist (Gadobutrol), NDA 201,277</b>	

**Total no. of pages including cover: 2**

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October 6, 2010

Regarding your pending NDA 201,277 for Gadovist, the clinical reviewer has the following information request.

For the 2 Pivotal Phase 3 studies, 310123 and 310124, please provide a listing of all subjects that received any dose of gadobutrol. Please list the weight of the subject and the dose administered.

Indicate the location of this source data in the NDA for purposes of inspection.

You should provide a response to this request via e-mail to [Barbara.Stinson@fda.hhs.gov](mailto:Barbara.Stinson@fda.hhs.gov) and cc me at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) by COB Friday October 22, 2010. Follow up your email response with a submission to your NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A  
Project Manager, DMIP

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/s/

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JAMES W MOORE  
10/06/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: October 5, 2010**

<b>To: Phillip Johnson</b>	<b>From: James Moore</b>
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number: (973) 487-2016</b>	<b>Fax number: (301) 796-9849</b>
<b>Phone number: (973) 487-2181</b>	<b>Phone number: (301) 796-2050</b>
<b>Subject: Clinical Request 4, Gadovist (Gadobutrol), NDA 201,277</b>	

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October 5, 2010

Regarding your pending NDA 201,277 for Gadovist (Gadobutrol) Injection the clinical team has the following comments and information requests.

The ISS refers to 57 subjects in the gadobutrol group who had clinically significant changes in ECG from baseline. Listing 24 in Appendix 5 is cited as the reference. Unfortunately, this table does not explain the changes in detail and does not relate whether changes are considered as AEs or whether changes are drug related.

Bayer also cites several tables listing subjects with various risk factors (mean values of QTcF less than or equal to 460 msec) but does not relate this to AEs or drug-related AEs in a summary fashion.

Provide relevant narratives for those subjects in the group of 57 listed who had clinically significant ECG changes attributed to the study drug.

Provide a summary of those subjects with potential risk factors who had a QTcF increase of 30 to 60 msec after baseline and the overall assessment of ECG, also, as above, for subjects where this may be treatment related.

This information was provided for 5 subjects in the Phase 1 studies. However, additional information is needed for these 5 subjects. Did any of them have treatment related changes and if they did what was the significance of the changes?

You should email your response to me at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) and follow up with a submission to your NDA. Provide the response to me by COB Tuesday, October 12, 2010.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

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JAMES W MOORE  
10/05/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: September 21, 2010**

<b>To: Phillip Johnson</b>	<b>From: James Moore</b>
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number: (973) 487-2016</b>	<b>Fax number: (301) 796-9849</b>
<b>Phone number: (973) 487-2181</b>	<b>Phone number: (301) 796-2050</b>

**Subject:** Statistical Request 1, Datasets, Tables, Gadovist (Gadobutrol), NDA 201,277

**Total no. of pages including cover: 9**

**Comments: These comments are draft and are subject to addition, deletion, or revision.**

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September 21, 2010

Regarding your pending NDA 201,277 for Gadovist, Gadobutrol, the statistical reviewer has the following comments and information requests.

The statistical reviewer has had difficulty deriving desired statistics from the submitted data sets. To facilitate and accelerate the review process, he is requesting the following:

**1. First: Several Tables and Statistics**

These should not be too difficult for Bayer staff familiar with the details of the NDA data sets to provide. The reviewer anticipates a relatively quick response to this request.

**2. Second: Data Sets**

These are critical to the conduct of a thorough analysis and validation of the results of the studies. The reviewer anticipates that this request will require a longer period of time to complete than the construction of the requested tables. A timely delivery of this material would be appreciated.

**Preliminary Notes on Tables/Statistics**

**(1):** *The Reviewer intends using this material to gain further insight into and understanding of the data; the material will not serve as the starting point and basis for formal statistics. Therefore, the fundamental unit to be summed in all cases is the Reader-Subject unit, as in the following example:*

*EnhancedNumber of X's = 10 could mean:  
Reader#1/Reader#2/Reader#3 respectively recorded 3/5/2 subjects as X*

**(2):** *“Enhanced” in all cases means Paired Unenhanced/ Enhanced.  
Thus Unenhanced versus Gadovist means:  
Unenhanced versus Paired Unenhanced plus Gadovist*

**To Begin:**

**First: A Set of 12 Tables for Visualized Lesions**

The three Visualization parameters were applied to a maximum of 5 lesions per subject per Imaging Modality, where Imaging Modality is denoted in the Table below as

U = Unenhanced Read; P = Paired Read.

The type of Table illustrated directly below will have entries determined by visualized lesions only. Each such table will be dedicated to a Visualization parameter, and to Unenhanced versus Paired Reads. (For the Cross- Over Study there will be a Table for Gadovist and another Table for ProHance; for the Gadovist-Only Study there will be a Gadovist table only.) The Table counts subjects over Readers. That is, the Reader results are pooled. The qualifying conditions are stated below:

***For Contrast Enhancement:***

U = J means:

A Subject had J lesions under the Unenhanced Read, each of whose individual scores  $\geq 3$

P = K means:

A Subject had K lesions under the Paired Read, each of whose individual scores  $\geq 3$

***For Border Delineation:***

U = J means:

A Subject had J lesions under the Unenhanced Read, each of whose individual scores  $\geq 3$

P = K means:

A Subject had K lesions under the Paired Read, each of whose individual scores  $\geq 3$

***For Internal Morphology:***

U = J means:

A Subject had J lesions under the Unenhanced Read, each of whose individual scores  $\geq 2$

P = K means:

A Subject had K lesions under the Paired Read, each of whose individual scores  $\geq 2$

N (I, J) = Number of cases (Subjects pooled across Readers) with U = J and P = K

*Note:* There is no requirement for “shared” lesions. A Subject can have U = 2 and P = 3, but the Unenhanced and the Paired Reads do not see the same lesions.

RDR#I	P = 0	P = 1	P = 2	P = 3	P = 4	P = 5	U Marginals
U = 0							
U = 1							
U = 2		N(2,1)					
U = 3							
U = 4							
U = 5					N(5,4)		
P Marginals							

There will be 6 tables for the Cross-Over Study and 3 tables for the Gadovist only Study

Three additional Tables for the Cross-Over Study follow the form indicated below, using the definitions above:

Set PG = Paired Gadovist ; PH = Paired ProHance

For each Reader, in the Cross-Over Study, and for each Visualization Endpoint

$N(I, J)$  = Number of cases (Subjects pooled across Readers) with  $PG=I$  ,  $PH = J$

RDR#I	PH =0	PH = 1	PH = 2	PH = 3	PH = 4	PH = 5	PG Marginals
PG = 0							
PG =1							
PG= 2		N(2,1)					
PG = 3							
PG = 4							
PG= 5					N(5,4)		
PH Marginals							

**Second: A Set of Statistics for all Detected Lesions**

**(A): For Cross-Over Study:** Provide Pooled Reader Min, Max, Quartiles , Mean, and Sigma for the Subject Level Numbers of Detected Lesions and N = Number of Contributing Reader Subjects for the three cases:

Unenhanced/ Gadovist Paired/ ProHance Paired Reads.

For instance: Gadovist Paired Pooled Reader Results might look like:

**Unenhanced Read;**

**N = 900; Min = 0; Max = 20; Quartile Left Endpoints = 0, 1.2, 3.5, 6.0 Mean = 5.2; Sigma = 4.5**

**(B):** Likewise, two sets of statistics for the Gadovist-Only Study

**Third: Tables of Pooled Reader –Subject Frequencies for Detected Lesions:**

**Cross-Over Study:**

Three Tables: Unenhanced/Gadovist Enhanced/ProHance Enhanced

**Gadovist-Only Study:**

Two Tables: Unenhanced/Gadovist Enhanced

In the Table: LJ = Pooled (Over readers) Number of Subjects with J Detected Lesions  
 LN= Pooled (Over readers) Number of Subjects with > Detected Lesions  
 Where LN is at most 10% of the overall number of cases.

Number of Detected Lesions	Pooled Reader Subject Frequencies
DL = 0	L0
DL= 1	L1
DL= 2	
DL = J	LJ
DL > N	L(>N)

**Cross-Over Study for Differences**

**Three Tables:**

**Gadovist - Unenhanced; Prohance - Unenhanced; Gadovist - ProHance**

**Gadovist-Only Study for Differences (One Table)**

In the Table: LK = Pooled (Over Readers) Number of Subjects with  
 Enhanced Read minus Unenhanced Read Detected Lesions = K  
 DL (< -M) Pooled (Over readers) Number of Subjects with Difference <-M constitutes at  
 most 5% of the cases, and DL (>N) also constitutes at most 5% of the cases.

Number of Detected Lesions	Pooled Reader Subject Frequencies
DL< -M	L(< -M)
DL= - M	L(-M)
DL= - (M -1 )	
DL = -1	L(-1)
DL = 0	L0
DL = 1	L1
DL = 2	
DL = K	LK
DL = N	LN
DL > N	L(>N)

**Fourth:**

**Start with the Cross-Over Study**

*Utilize categories of Numbers of lesions determined by the Unenhanced Reads*

For X = Unenhanced (U); = Paired Gadovist (PG) ; = Paired Prohance (PH)

For each Reader-Subject:

X = 0 means Read X detected 0 lesions in the Subject

X = 1 means # Lesions detected under Read X was > 0, but in First Unenhanced Quartile

X = 2 means # Lesions detected under Read was in Second Unenhanced Quartile

X = 3 means # Lesions detected under Read was in Third Unenhanced Quartile

X = 4 means # Lesions detected under Read was in Fourth Unenhanced Quartile

Then, for Pooled Readers: (Three Tables)

Provide U versus PG; U versus PH; PG versus PH Tables for Cross- Over Study

**Example: U versus PG**

N (I, J) represents the number of cases (All subjects over three Readers) where

U had a Lesion Count found in the Unenhanced Second Quartile and PG had a Lesion Count> 0 and found in the First Unenhanced Quartile.

	PG = 0	PG = 1	PG = 2	PG = 3	PG = 4	U Marginals
U = 0						
U = 1						
U = 2		N(2,1)				
U = 3						
U = 4						
PG Marginals						

*Then: Provide U versus PG Table for the Gadovist-Only Study (One more Table)*

**Requested Data Sets for NDA201277**

**Requested Data Set#1: (Study A47567)**

The data set will be restricted to the FAS population.

Each subject will have three lines of data, one for each of the three visualization parameters:

Contrast Enhancement; Border Delineation; Internal Morphology

Each of the three lines of data for the subject will then have duplicate columns (A) and (B) as follows:

(A): First 8 Columns: Country/Center/Center Subject/Subject ID/Machine Type/Age/Race/Gender

(B): Next 7 columns:

- Referral Region (Brain and/or Spine)
- Referral (Subject Level) Diagnosis (e.g., Pineal Gland Tumor)
- Local Region Implicated in the Subject Level Diagnosis (e.g., Brain Stem)
- Non-Study Related Imaging used in the Final Diagnosis
- Standard of Truth Subject Level Diagnosis
- Classification of “Primary” Lesion (Benign/Malignant )
- Classification of Subject as Normal/Abnormal for Brain Tissue

Again, these first 15 columns will be identical on all three lines dedicated to a particular subject.

The next columns are groups of variables, with each group dedicated to results for the following

Nine Reader/Image Types:

- Blinded Reader#1 Unenhanced Columns
- Blinded Reader#1 Paired Unenhanced plus Gadovist Columns
- Blinded Reader#1 Paired Unenhanced plus ProHance Columns
- Blinded Reader#2 Unenhanced Columns
- Blinded Reader#2 Paired Unenhanced plus Gadovist Columns
- Blinded Reader#2 Paired Unenhanced plus ProHance Columns
- Blinded Reader#3 Unenhanced Columns
- Blinded Reader#3 Paired Unenhanced plus Gadovist Columns
- Blinded Reader#3 Paired Unenhanced plus ProHance Columns

The variables under each of the nine Reader/Image Types are:

First Set of Variables is dedicated to Normal Structures free of lesions:

- Variable#1: Number of Normal Brain Structures without Lesions
- Variable#2: Sum of Visualization Scores over these Lesion Free Normal Brain Structures
- Variable#3: Denominator used for calculating the Average Lesion Free Normal Structure Score
- Variable#4: Average Normal Structure Visualization Score= $\text{Variable\#2}/\text{Variable\#3}$

Next:

- Variable#5: Total Number among Variable#1 with Contrast Scores  $\geq 3$
- Variable#6: Total Number among Variable#1 with Border Delineation Scores  $\geq 3$
- Variable#7: Total Number among Variable#1 with Internal Morphology Scores  $\geq 2$

The next Set of Variables is dedicated to lesions that contribute to the visualization results:

- Variable#8: Number of Detected Lesions ( $\leq 5$ ) that contribute to the Lesion Visualization Score
- Variable#9: Sum of Lesion Scores that contribute to the Lesion Visualization Score
- Variable#10: Denominator used for Average Lesion Visualization Score
- Variable#11: Average Lesion Visualization Score =  $\text{Variable\#9}/\text{Variable\#10}$

Next:

Variable#12: Total Number among Variable#8 with Contrast Scores  $\geq 3$

Variable#13: Total Number among Variable#8 with Border Delineation Scores  $\geq 3$

Variable#14: Total Number among Variable#8 with Internal Morphology Scores  $\geq 2$

Then:

Variable#15: Average Visualization Score =  $(1/2)$  (Variable#4 + Variable#11)

Finally for the Lesion Detection Endpoint and for Diagnoses:

Variable#16: Total Number of Detected Lesions

Variable#17: Subject Level Classification of “Primary” Lesion as Benign/Malignant

Variable#18: Subject Level Diagnosis

Variable#19: Subject Level Classification of Brain Tissue (Normal/Abnormal)

Variable#20: Classification of Diagnosis as Match/Mismatch with Truth

*Note: The Submission indicates that these Brain Tissue classifications for the Cross-Over Study do not involve either Paired Reads or Unenhanced Reads. The classifications can be placed in the Paired Read columns with the understanding that they represent Enhanced T1 Reads only.*

Final Columns – After all nine groups of columns listed above:

Three additional groups of columns, a group for each Image Type:

Unenhanced; Paired Unenhanced plus Gadovist; Paired Unenhanced plus ProHance.

The variables under each Type will be Across-Reader Averages and Majority Reads:

Variable#1: Across Readers Average Visualization Score for Normal (Lesion Free) Regions

Variable#2: Across Readers Average Visualization Score for Visualization Lesions

Variable#3: Combined (Normal plus Lesion) Across Reader Visualization Score

Variable#4: Across Reader Average Number of Lesions detected

Variable#5: Majority Read Subject Level Classification of “Primary” Lesion as Benign/Malignant

Variable# 6: Majority Read Subject Level Diagnosis

Variable# 7: Majority Read Subject Level Classification of Brain Tissue (Normal/Abnormal)

Variable# 8: Majority Read Classification of Diagnosis as Match/Mismatch with Truth

***Comments:***

***(1): The Reviewer counts a total of 219 columns***

***(2): Numerical rather than Character columns are preferred***

**Requested Data Set#2: (Study A47570)**

***Same as Data Set#1, except for absence of ProHance data.***

The reviewer is available for a TCON to discuss the details in this request, which should include the Sponsor's estimates of the time required for providing parts of the desired material. A TCON would also clarify whether the reviewer's understandings of some aspects of the data is correct.

The information should be provided as soon as it is available.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

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JAMES W MOORE  
09/21/2010



**Food and Drug Administration  
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Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** August 30, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Clinical Request 3, Gadovist (Gadobutrol), NDA 201,277, Clinical Site Address	

**Total no. of pages including cover:** 2

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August 30, 2010

Regarding your pending NDA 201, 277 for Gadovist (Gadobutrol), study 310124, site 14004, you should provide the following information.

1. Name of Contact-Jae Kim, Site Address, Email address of contact, contact telephone number.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

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GADOBUTROL INJECTION

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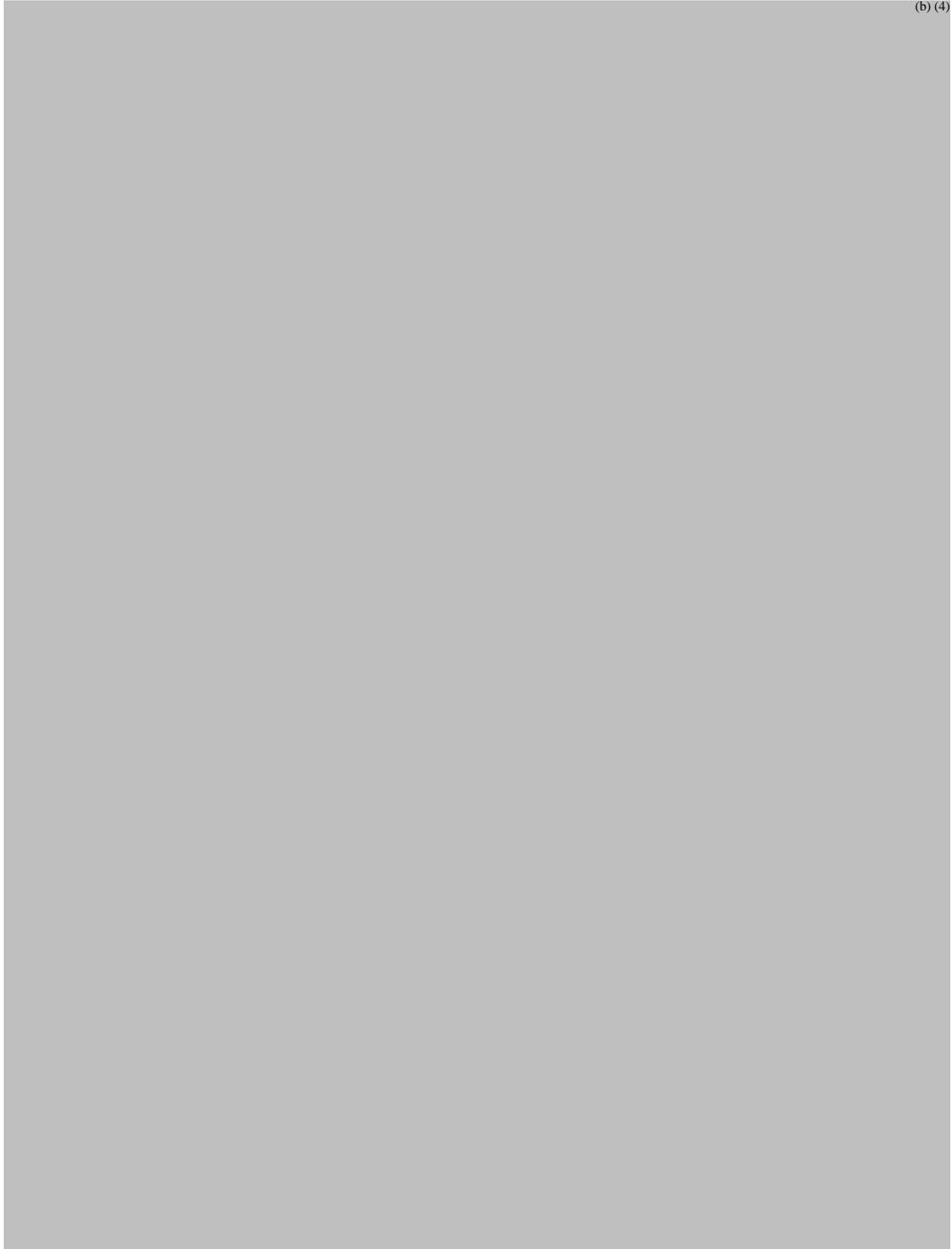
/s/  
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JAMES W MOORE  
08/30/2010

August 12, 2010

Regarding your pending NDA 201,277 for Gadovist (Gadobutrol), the reviewing microbiologist has the following comments and requests.

Please provide the following information or a reference to its location in the current submission:



2. [REDACTED] (b) (4)
3. Provide a summary of all routine in-process bioburden testing, the bioburden limit, and actions to be taken should the bioburden be exceeded.
4. Provide the names of the suppliers and the item numbers for all components of the container-closure systems for the vials and bottles in this application.
5. Provide a description of the positive controls used during container-closure integrity testing. [REDACTED] (b) (4)
6. Provide a summary of the environmental monitoring program for the [REDACTED] (b) (4) location.
7. Include [REDACTED] (b) (4) as a manufacturer in Module 3.2.P.3.1 and any other relevant sections of the NDA.
8. Provide a description of the controls to minimize microbial contamination of the bulk storage solution and the pre-sterilized, filled syringes during shipping between Bayer [REDACTED] (b) (4).
9. Describe the minimum and maximum loads for Inv. No. 122103 and 122107. Indicate whether all three [REDACTED] (b) (4) will be used for each product configuration or whether there are [REDACTED] (b) (4) for particular load types.
10. Provide the [REDACTED] (b) (4) acceptance criteria for production runs to include, for example, [REDACTED] (b) (4). Clearly define any critical or key process parameters for Inv. No. 139997, 122103 and 122107 with loads containing vials, bottles, and pre-filled syringes. Provide the actions to occur should these parameters not be met.
11. Provide a description of the methods used to control [REDACTED] (b) (4)
12. Indicate the location of the fixed temperature sensors in each [REDACTED] (b) (4).



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201277	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	GADOBUTROL INJECTION

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JAMES W MOORE  
08/12/2010



Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

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GADOBUTROL INJECTION

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JAMES W MOORE  
08/06/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** August 3, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Clinical Request 2, Gadovist (Gadobutrol), NDA 201,277, Clinical Site Addresses	

**Total no. of pages including cover:** 2

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**Document to be mailed:**             YES                             NO

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August 3, 2010

This is a follow-up request to the clinical request of July 13, 2010 for pending NDA 201,277 for Gadovist (Gadobutrol).

Bayer provided a listing of sites by number and location (the 2 pivotal studies) however, no addresses were provided and the NDA does not contain this information.

Please provide the addresses for sites 10006, 14002 (study 310123), site 14001 (study 310124) and the address of the <sup>(b) (4)</sup> (Blinded read) facility in <sup>(b) (4)</sup>.

You should provide this information to me via email at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) by COB Thursday, August 5, 2010. You should follow up your e-mail submission with a submission of the information to your pending NDA.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

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GADOBUTROL INJECTION

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/s/  
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JAMES W MOORE  
08/03/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Pediatric and Maternal Health  
Staff/Maternal Health Team**

FROM (Name, Office/Division, and Phone Number of Requestor):  
**James Moore, PM (301) 796-1986, Barbara Stinson,  
MDO, 796-1470**

DATE  
**August 2, 2010**

IND NO.  
**56,410**

NDA NO.  
**201-277**

TYPE OF DOCUMENT  
**New NDA**

DATE OF DOCUMENT  
**May 14, 2010**

NAME OF DRUG  
**Gadovist (Gadobutrol)**

PRIORITY CONSIDERATION  
**Moderate**

CLASSIFICATION OF DRUG  
**1S**

DESIRED COMPLETION DATE  
**November 2, 2010**

NAME OF FIRM: **Bayer HealthCare Pharmaceuticals**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** This is a New Drug Application. It is a gadolinium based contrast agent that will be used for magnetic resonance imaging (MRI) of the central nervous system (CNS). Please review sections of the proposed label as they relate to pregnancy and lactation. This submission can be found under NDA 201-277 in the EDR. The labeling can be found in the Labeling Folder (1.14) and several subfolders (1.14.1, 1.14.4, 1.14.5).

SIGNATURE OF REQUESTOR  
**James Moore**

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

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GADOBUTROL INJECTION

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/s/  
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JAMES W MOORE  
08/02/2010



NDA 201-277

**FILING COMMUNICATION**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Phillip Johnson  
Deputy Director, Global Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Dear Mr. Johnson:

Please refer to your new drug application (NDA) dated May 14, 2010, received May 14, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Gadovist 1.0 (Gadobutrol) Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is March 14, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 23, 2011.

During our filing review of your application, we identified the following potential review issues:

**CLINICAL**

1. The proposed strength of your diagnostic drug is 1 M (one molar) as compared to other available gadolinium based drugs which are 0.5 M (half molar). We are concerned that this difference might lead to potential errors in administration of your drug. Such a medication error may be especially harmful to a patient with end-stage renal failure or with an acute kidney injury.

2. Our preliminary examination of your application suggests that the labeling will need modification to help minimize the risk for medication errors due to the molarity difference cited above. We encourage you to develop labeling proposals to address this concern and submit a proposal as soon as possible. For example, you may wish to consider an alternative proprietary drug name along with more explicit and prominent text within the prescribing information.

### **MICROBIOLOGY**

3. The leaf titles in Module 3 (and perhaps other Modules) are not consistent with the current recommendations on CDER eCTD submissions. All future submissions should include a descriptive leaf title and not simply a study number. If you have any questions please contact the CDER Electronic Submission Support team at [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov) or visit the eCTD website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have not already done so, you must 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application (children 2 years of age and below). Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796-2050.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201277	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	GADOBUTROL INJECTION

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/s/

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JAMES W MOORE  
07/30/2010

IRA P KREFTING  
07/30/2010

Acting Division Director. Dr. Rieves, Division Director, is on leave.

Memo to the File:

Date: July 23, 2010

Subject: Orientation Briefing, Gadovist, NDA 201-277

Applicant: Bayer HealthCare Pharmaceuticals (Bayer)

The following list of FDA staff attended the Applicant Orientation Briefing on July 15, 2010. At the request of Bayer HealthCare Pharmaceuticals this listing was send via e-mail to them today.

Rafel Rieves, M.D., Director, DMIP  
Scheldon Kress, M.D., Clinical Reviewer, DMIP  
Lucie Yang, M.D., Ph.D., Clinical Reviewer, DMIP  
Qi Feng, M.D., Clinical Reviewer, DMIP  
Barbara Stinson, D.O., Clinical Reviewer, DMIP  
Joseph Kaminski, M.D., Clinical Reviewer, DMIP  
Olayinka Dina, Ph.D., D.V.M., Pharmacology/Toxicology Reviewer, DMIP  
Ross Filice, M.D., Clinical Reviewer, DMIP  
Shari Targus, M.D., Acting Deputy Director, DMIP  
Sally Hargus, Ph.D., Pharmacology/Toxicology Reviewer, DMIP  
Shaw Chen, M.D., Deputy Office Director, ODEV IV  
Rene Tyson, M.S., Safety Project Manager, DMIP  
Susan Johnson, PharmD., Ph.D., Associate Deputy Director, ODEV IV  
Eric Duffy Ph.D., Director, DNDQA  
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, ONDQA  
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, OCP  
Ira Krefting, M.D., Medical Officer, Safety, DMIP  
Anthony Mucci, Ph.D., Statistical Reviewer, OB  
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB  
Louis Marzella, M.D., Ph.D., Clinical Team Leader, DMIP  
Alexander Gorovets, M.D., Clinical Team Leader, DMIP  
James Moore, PharmD., M.A., Project Manager, DMIP  
Ali Al-Hakim, Ph.D., Branch Chief, ONDQA  
Jessica Cole, Ph.D., Microbiology Reviewer, OPS

James Moore, PharmD., M.A.  
Project Manger, DMIP

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

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GADOBUTROL INJECTION

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/s/  
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JAMES W MOORE  
07/23/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** July 14, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer HealthCare	Division of Medical Imaging Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050

**Subject:** Clinical Pharmacology Request 1, Datasets, Gadovist (Gadobutrol), NDA 201,277

**Total no. of pages including cover:** 2

**Comments:** These comments are draft and are subject to addition, deletion, or revision.

**Document to be mailed:**             YES                     NO

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July 14, 2010

Regarding your pending NDA 201, 277 for Gadovist the reviewing clinical pharmacologist has the following request.

1. Please submit the data set, NONMEM control streams (base, covariate and final models) and the output listing for the population PK analysis (Module 5.3.3.5) as soon as possible.

We encourage the Applicant to refer to the following pharmacometric data and models submission guidelines.

(<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>):

All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.  
Project Manager, DMIP

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

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GADOBUTROL INJECTION

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/s/  
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JAMES W MOORE  
07/14/2010

July 13, 2010

Regarding your pending NDA 201, 277 for Gadovist (Gadobutrol) and each of your Phase 3 pivotal trials, please provide the following information by site.

1. The number of patients at each site.
2. The number of Adverse Events at each site.
3. The number of Serious Adverse Events at each site.
4. The number of protocol violations at each site.
5. The number of patient withdrawals at each site.

You should provide this information to the Division by COB Tuesday, July 20, 2010.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD, M.A.  
Project Manager, DMIP

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
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GADOBUTROL INJECTION

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/s/  
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JAMES W MOORE  
07/13/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): ODS

FROM (Name, Office/Division, and Phone Number of Requestor): James Moore, PM (301) 796-1986, Barbara Stinson, Clinical Reviewer (301) 796-1470, DMIP

DATE  
June 10, 2010

IND NO.  
56,410

NDA NO.  
201-277

TYPE OF DOCUMENT  
consult, safety evaluation

DATE OF DOCUMENT  
June 10, 2010

NAME OF DRUG  
Gadovist

PRIORITY CONSIDERATION  
High

CLASSIFICATION OF DRUG  
1S

DESIRED COMPLETION DATE  
November 2, 2010

NAME OF FIRM: Bayer HealthCare Pharmaceuticals, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING              | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING      | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING       | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION                 | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA                    | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT           |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** This product is a gadolinium based contrast agent(GBCA). Its proposed indication is evaluation of CNS lesions with MR technology. The DMIP is requesting that you evaluate the risk management plan submitted in the NDA to determine if the plan as proposed is comprehensive enough to effectively evaluate the safety risks of this product. In addition, please provide any comments on the possible safety risks of the product that you find during this assessment. This is an electronic submission and the application may be found in the electronic document room under NDA 201-277 (Gadovist). The risk assessment plan is located in folder 1.16 and the file name is us-risk-management-plan.pdf. The PDUFA date is March 14, 2011.

SIGNATURE OF REQUESTOR  
James Moore

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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JAMES W MOORE  
09/28/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: June 8, 2010**

<b>To: Phillip Johnson</b>	<b>From: James Moore</b>
<b>Company: Bayer HealthCare</b>	Division of Medical Imaging Products
<b>Fax number: (973) 487-2016</b>	<b>Fax number: (301) 796-9849</b>
<b>Phone number: (973) 487-2181</b>	<b>Phone number: (301) 796-2050</b>

**Subject:** Meeting Confirmation, Applicant Orientation Briefing, Gadovist (Gadobutrol), NDA 201,277

**Total no. of pages including cover: 3**

**Comments:**

**Document to be mailed:**       YES       NO

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June 8, 2009

Please refer to your pending New Drug Application (NDA 201,277) for Gadovist (Gadobutrol). This correspondence confirms that an Applicant Orientation Briefing has been scheduled with Bayer and FDA so that Bayer may present certain data/information from the Application to the Agency. Here are the meeting details.

Date: Thursday, July 15, 2010

Time: 1:00 PM - 2:30 PM

Location: FDA White Oak Campus, Building 22, Conference Room 1419, 10903 New Hampshire Avenue, Silver Spring, Maryland 20903

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance.

Please send a list of meeting attendees to me at least 7 days before the meeting.

I have also attached a form that must be completed for each non U.S. citizen attending this meeting. Entries on the form must be clearly legible. Please complete this form and return it to me as soon as possible but no later than 2 weeks prior to the meeting.

If you have any questions, call me at (301) 796-2050.

Sincerely,

James Moore, PharmD., M.A.  
Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

## FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

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GADOBUTROL INJECTION

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/s/  
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JAMES W MOORE  
07/15/2010



NDA 201, 277

**NDA ACKNOWLEDGMENT**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Phillip Johnson  
Deputy Director, Global Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Dear Mr. Johnson:

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: Gadovist (Gadobutrol) 1M Injection

Date of Application: May 14, 2010

Date of Receipt: May 14, 2010

Our Reference Number: NDA 201, 277

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 July 13, 2010 in accordance with 21 CFR 314.101(a).

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

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

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

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If you have any questions, call me at (301) 796-2050.

Sincerely,

*{See appended electronic signature page}*

James Moore, PharmD., M.A.  
Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201277

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ORIG-1

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BAYER  
HEALTHCARE  
PHARMACEUTICA  
LS INC

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GADOBUTROL INJECTION

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/s/  
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JAMES W MOORE  
06/08/2010



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 26, 2010

<b>To:</b> Phillip Johnson	<b>From:</b> James Moore
<b>Company:</b> Bayer Healthcare	Division of Medical Imaging and Hematology Products
<b>Fax number:</b> (973) 487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (973) 487-2181	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Meeting Minutes, I 56,410 Gadovist, 2-4-2010	

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**Total no. of pages including cover:** 20

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**Comments:**

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**Document to be mailed:**       YES       NO

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Industry Meeting between the Division of Medical Imaging and Hematology and Bayer HealthCare, Thursday, February 4, 2010, White Oak Campus, Building 22, Conference Room 1421, Silver Spring, Maryland 20903

Subject: Gadobutrol (Gadovist) Pre NDA Meeting I 56,410

**Bayer Healthcare Attendees:**

Phillip Johnson, Deputy Director, Global Regulatory Affairs  
Christine Becker, Head Diagnostic Imaging, Global Regulatory Affairs  
Thomas Balzar, M.D., Vice President and Head, Global Clinical Development  
Martin Rosenberg, M.D, Senior Director, Global Clinical Development  
Harold Goldstein, M.D., Vice President, US Medical Affairs  
Daniel Haverstock, PhD., Principal Statistician, Clinical Statistics  
Marcus Schultz-Mosagu, PhD., Specialist, Clinical Pharmacology  
Mary Shaw, PhD., Senior Toxicologist, Nonclinical Drug Safety  
Rita Darkow, M.D., Global Project Leader, Global Project Management

**FDA Attendees:**

Rafel Rieves, M.D., Director, DMIHP  
Alexander Gorovets, M.D., Clinical Team Leader, DMIHP  
Barbara Stinson, D.O., Clinical Reviewer, DMIHP  
Young Moon Choi, PhD., Team Leader, Clinical Pharmacology, OCP  
Christy John, PhD., Clinical Pharmacology Reviewer, OCP  
Anthony Mucci, PhD., Statistical Reviewer, OB  
Jyoti Zalkikar, PhD., Statistical Team Leader, OB  
Eldon Leutzinger, PhD., Pharmaceutical Assessment Lead, ONDQA  
Vinayak Pawar, PhD., Microbiology Reviewer, OPS  
Adebayo Lanionu, PhD., Pharmacology Toxicology Team Leader, DMIHP  
James Moore, PharmD., M.A., Project Manager, DMIHP  
Melanie Freed, Engineer, CDRH

**Background**

This Pre-NDA Meeting was requested by Bayer. Prior to the meeting a response to Bayer's questions contained in their Meeting Package of December 23, 2009 was sent to them. A copy of the responses provided to Bayer appears below. After introductions the meeting began.

February 2, 2010

We are providing these preliminary comments in preparation for our face-to-face meeting scheduled for February 4, 2010. These comments should not be considered as an official FDA position. They are meant to promote and facilitate a collaborative and successful exchange at the upcoming meeting. The minutes of the meeting will reflect the

discussion that will take place at the meeting and might not be consistent with these preliminary comments.

We refer to your IND 56, 410 for Gadovist (Gadobutrol) and your meeting package dated December 23, 2009. We have reviewed the submitted information and are providing draft responses to your questions. These responses were provided to Mr. Phillip Johnson on Tuesday, February 2, 2010 (Your questions are presented further below in italics and are then followed by our responses in bold).

### Clinical Questions

#### Supportive Clinical Studies and Financial Disclosures

*The submission of a NDA for Gadobutrol for the proposed indication will be based on the 2 pivotal Phase 3 studies 310123 and 310124. Clinical efficacy data from the Phase 2 study 308200 and the Japanese Phase 2/3 study 310864 will be analyzed along with the 2 pivotal studies and presented in the Integrated Summary of Efficacy. Additionally, the use of Gadobutrol in the pediatric population ages 2 – 17 will be based on the results of study 310788. The discussion of these 5 studies will comprise the majority of the Integrated Summary of Efficacy.*

*Bayer considers the remaining 38 clinical studies listed in Appendix 1 as “supportive” and we intend to place most of these studies in Module 5.3.5.4 (“Other Reports of Efficacy and Safety”) of the eCTD. As noted above, these supportive clinical studies consist mostly of Phase 1 – 3 studies that were conducted earlier to support the registration of Gadobutrol in Europe and other countries, and many of these studies were conducted using an earlier formulation (0.5 mmol/ml) of Gadobutrol. See Appendix 1 for the listing of the studies and their respective placement within the eCTD structure.*

*Bayer considers the pivotal studies 310123, 310124, 308200, 310864 and 310788 to be “covered clinical studies” as defined by FDA’s “Guidance for Industry – Financial Disclosure by Clinical Investigators, March 2001” and will therefore submit FDA Forms 3454 and 3455 for these studies. The remaining supportive studies, as listed in Appendix 1 are studies in which Bayer is not substantially relying upon to support the use of Gadobutrol for its proposed indication. Therefore, Bayer does not plan to submit Financial Disclosure documentation for these studies.*

*Sponsor's Question 1a:*

*Does FDA agree with the placement of these studies in the eCTD structure?*

*Sponsor Question 1b:*

*Does FDA agree with Bayer’s assessment of studies that will be considered “covered clinical studies”?*

### **FDA's Response 1a & 1b:**

**It is premature to comment on the placement of studies in the eCTD structure as you have not provided sufficient information in reference to your studies. Specifically, you have provided no information on study 310864 and no updated information on study 310123. We recommend that you provide the rationale for placing a particular study in the Integrated Summary of Efficacy (ISE) and clarify the reasons for not placing a study in the ISE for each of the remaining studies. Pending these clarifications and the results of the efficacy analyses of studies 310123 and 310864 the proposal to group the five clinical studies to show substantial evidence for effectiveness and to consider the remaining 38 studies as supportive might be acceptable.**

#### *Integrated Summaries of Efficacy and Safety*

*Bayer will be providing both an Integrated Summary of Safety and an Integrated Summary of Efficacy in Module 5.3.5.3 of the eCTD structure. Below is a summary of the planned analyses in these documents.*

#### *Safety*

*For the integrated analysis of safety, the following data pools will be created:*

- *All Phase 2 – 4 studies for Gadobutrol, including 12 Phase 2 studies, 19 Phase 3 studies, 1 Phase 1/3 study, 1 Phase 2/3 study, and 1 Phase 4 study. Twenty (20) of the included studies are single arm Gadobutrol studies, 9 have a parallel group design with either different Gadobutrol doses or Gadobutrol and a comparator contrast agent, and 5 are cross-over studies with either different Gadobutrol doses or Gadobutrol and a comparator contrast agent. Comparators are Magnevist (Gadopentetate-Dimeglumine), Omniscan (Gadodiamide), OptiMark (Gadoversetamide) or ProHance (Gadoteridol). Appendix 1 provides a listing of all included studies.*

*The above pool, consisting of approximately 5545 patients (4300 of which received Gadobutrol) will serve as the primary basis for the development of Section 6 (Adverse Reactions) of the US Package Insert.*

- *All Phase 1 studies for Gadobutrol.*

*The primary focus of the Integrated Summary of Safety will be on the clinical safety of Gadobutrol. In addition, comparisons to other approved MRI contrast agents, studied in head to head trials, will be provided.*

*Key analyses for safety will consist of*

- *Number and incidence of adverse events, drug-related adverse events, serious adverse events, and drug-related serious adverse events.*
- *Comparison of vital signs between pre and post injection.*
- *Comparison of laboratory parameters between pre and post injection.*
- *Analysis of subgroups, e.g. gender, age categories, race, risk population e.g. impaired renal function, liver function, important current diseases*

*In addition, a summary of post-marketing adverse events, based on reports in Bayer's global pharmacovigilance database for Gadobutrol, will be provided and discussed in the Integrated Summary of Safety.*

### *Efficacy*

*The primary focus of the Integrated Summary of Efficacy will be on the comparison of the efficacy of MRI enhanced with Gadobutrol 1.0 mmol/kg compared to unenhanced MRI.*

Confirmation of efficacy will be based primarily on the analysis in 2 pivotal phase 3 studies (310123 and 310124). The following primary variables were evaluated by two different sets of 3 independent blinded readers in these two studies:

### *Superiority*

- *Degree of contrast enhancement*
- *Assessment of border delineation*
- *Internal morphology of lesions*

### *Non-inferiority*

- *Total number of lesions detected.*

*An important secondary variable analyzed in both these studies was*

- *Exact match of the MR diagnoses with the final clinical diagnosis*

*This variable was analyzed for accuracy and also sensitivity and specificity for two conditions (presence of any abnormal tissue and presence of a malignant lesion).*

*Study 310123 included evaluations of the preceding variables for ProHance. An important secondary comparison for these and other secondary efficacy variables will be performed in a non-inferiority analysis of Gadovist to ProHance.*

*The justification of the dose used in the pivotal phase 3 studies is primarily based on the analyses from the Phase 2 study 308200.*

*Supplemental efficacy analyses will be performed on pooled data from several studies. For the integrated analyses of efficacy, the following data pools will be created for selected key variables:*

- The first pool consists of the two pivotal Phase 3 studies 310123 and 310124, as well as the Phase 2 study 308200. All results from subjects who received 0.1 mmol/kg Gadobutrol (or comparator) will be included in this analysis, while patients receiving doses of Gadobutrol other than 0.1 mmol/kg (in the Phase 2 study) will not be pooled.*
- The second pool consists of the 3 studies in the first pool, plus the Japanese Phase 2/3 study 310864. In this pool, all results from subjects who received 0.1 mmol/kg Gadobutrol (or comparator) and who were assessed for a malignant diagnosis will be analyzed.*

*Efficacy results from all other studies will be summarized in the ISE but no formal integration of efficacy will be performed. Complete study reports for these additional supportive studies will be placed in Module 5.3.5.4 of the eCTD structure.*

#### Pediatrics

*A discussion of the pharmacokinetics and safety of Gadobutrol in children ages 2 – 17 years from study 310788 will be provided in the Integrated Summaries of Safety and Efficacy.*

- 2. Does FDA agree with the proposed data pools and key analyses that will be included in the ISE & ISS?*

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

**We generally agree with the proposed data pools and analyses that you plan to include in the ISE & ISS.**

**Please clarify the reason for the placement of nine Phase 1 studies in a separate data pool for safety analysis and confirm that safety analyses will include all subjects/patients receiving at least one dose of gadobutrol.**

**Please clarify the methodology for analysis of the variables for each of the studies where pooled data are being used. We note that the design of the Phase 2 dose ranging study (study 308200) might differ from the “pivotal” Phase 3 studies in the approach to lesion scoring and analysis.**

#### Biostatistical Question

##### Statistical and Electronic Datasets

*The Gadobutrol eCTD submission will contain 2 types of datasets, both to be submitted electronically in SAS Version 5 transport file format with corresponding documentation:*

- **SDTM datasets** (version 3.1.1) with *define.xml* documentation [*.xml* style sheet, and the annotated CRF (*blankcrf.pdf*)] to be placed in the “Data Tabulation” section of the eCTD
- **Bayer analysis datasets** with *define.pdf* documentation to be placed in the “Analysis” section of the eCTD

*There are a large number of individual clinical study reports that will be included in the submission reflecting the comprehensive development program conducted to date in phases 1 – 4. Specific protocol numbers and a short description of the study design of each of these studies are listed in the Appendix 1. We will submit Bayer analysis datasets to accompany each of the studies listed. The Bayer analysis datasets contain all raw data as it was collected from the clinical trial CRF's as well as additional derived variables and derived datasets created specifically to support study analysis. All statistical programs written in SAS for statistical table generation utilized these **Bayer** analysis datasets as input.*

*In addition, integrated efficacy and safety analyses will be conducted. Two integrated safety pools will be provided: a pool of phase 1 studies (conducted in healthy volunteers), and a separate pool of all Phase 2 – 4 studies. An integrated efficacy pool will also be provided containing data from studies 310123, 310124, 310864, and 308200 (the 2 Phase 3 studies, the Phase 2/3 Japanese study, and the Phase 2 study). Bayer analysis datasets will be provided for these pooled efficacy and safety analyses.*

*To assist in medical review of the eCTD, we propose to submit data in SDTM (version 3.1.1) format for the following clinical studies. These studies are:*

- *the two phase 3 pivotal studies: Protocols 310123 and 310124*
- *phase 2/3 study conducted in Japan: Protocol 310864*
- *phase 2 study: Protocol 308200*
- *pediatric study conducted in the EU and Canada: Protocol 310788*

*Case report forms for patient deaths and drop-outs due to adverse events will be provided for all clinical studies. All other case report forms will be available upon request.*

*Sponsor's Question 3:*

*Does the Agency agree with the proposal outlined above regarding the scope, format, and documentation of the electronic datasets to be submitted?*

**FDA's Response 3:**

**The Agency is in agreement with the proposed data set submissions. Once the submission is in house, there may be requests from the statistical reviewer for a few additional derived data sets whose formatting could facilitate the review process and whose preparation would be time efficient if prepared by the Sponsor rather than the reviewer.**

Clinical Pharmacology Questions

*Clinical pharmacology studies were performed with Gadobutrol to investigate safety, tolerability and pharmacokinetics in healthy adults, special populations and patients as described in Table 1 below.*

**Table 1 – List of Clinical Pharmacology Studies**

<b>Study No.</b>	<b>Study</b>	<b>Product and dose</b>	<b>Location of report</b>
Healthy subjects			
98098	Intraindividual controlled, randomized, crossover concentration comparison study of 0.5 and 1.0 molar gadobutrol injection in MR brain perfusion imaging in healthy volunteers	SH L562 AA + SH L562 BB 0.3 mmol/kg	5.3.5.4
96063	Pilot study in healthy volunteers on bolus geometry, resulting from different application schemes and dosages	SHL562A + SHL562BB 0.05, 0.1, 0.2 mmol/kg	5.3.5.4
310865	Japanese single-dose safety, tolerability, pharmacokinetic and divided dose study in healthy Japanese adult men	SH L562BB 0.1, 0.2, 0.3 and 0.1+0.1 mmol/kg	5.3.3.1.1
97113	Single-dose safety, tolerability and pharmacokinetic study in healthy Caucasian adult men	SH L562BB 0.3, 0.5, 0.75, 1.0, 1.25 and 1.5 mmol/kg	5.3.3.1.2
307362	Thorough QT study in healthy adults of different ethnicities (USA) including pharmacokinetics	SH L562BB 0.1, 0.3 and 0.5 mmol/kg	5.3.3.1.3
93016	Japanese single-dose safety, tolerability and pharmacokinetics study in healthy Japanese adult men	SH L562A 0.05, 0.1, 0.2 and 0.4 mmol/kg	5.3.3.1.5
92001	Single-dose safety, tolerability and pharmacokinetics study in healthy Caucasian adult men	SH L562A 0.04, 0.1, 0.2, 0.3, and 0.4 mmol/kg	5.3.3.1.5
Special populations			
95062	Single-dose safety and tolerability Phase 3 study in patients with renal impairment including pharmacokinetics	SH L562BB 0.1 and 0.3 mmol/kg	5.3.3.3

91798	Single-dose safety, tolerability and pharmacokinetics study in healthy non-elderly and elderly male and female healthy subjects	SH L562BB 0.1 mmol/kg	5.3.3.3
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Pediatric patients

310788	Single dose Phase I/III study in pediatric patients aged 2-17 years	SH L562BB 0.1 mmol/kg	5.3.5.1
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SH L562BB: product with 1.0 mmol/mL gadobutrol as an active ingredient

SH L562A: product with 0.5 mmol/mL gadobutrol as an active ingredient

*Sponsor's Question 4:*

*Bayer believes that the above clinical pharmacology program summarized above adequately supports the submission of an NDA for Gadobutrol. Does the Agency agree?*

**FDA's Response 4:**

**The clinical pharmacology studies performed by the sponsor as listed in Appendix 1 and clinical pharmacology studies in special populations appear adequate for the submission of an NDA for Gadobutrol. Please note, however, that the acceptability of the data is a review issue. Please submit all the individual data electronically.**

**In order for the QT IRT to review the Thorough QT Study Report of Study 307362, and to accelerate the review process, the following items should be submitted:**

- **Electronic copy of the study report**
- **Electronic or hard copy of the clinical protocol**
- **Electronic or hard copy of the Investigator's Brochure**
- **Annotated CRF**
- **Copies of the study reports for any other clinical QT study for this product that has been performed**
- **A Define file which describes the contents of the electronic data sets**
- **Electronic data sets as SAS transport files**
- **Please make sure that the ECG raw data set includes at least the followings: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, intervals (QT, RR, PR, QRS), HR, QTc [all corrected QT as end points, e.g. QTcB, QTcF, QTcI (including individual correction factor), or QTcN (including the correction factor)], Lead, ECG ID (link to waveform files if applicable).**
- **SAS code for the primary statistical analysis**
- **Data set whose QT/QTc values are the average of the replicates**
- **Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis**
- **Narrative summaries and case report forms for any of the following that occur in this thorough QT study:**
  - i. **Deaths**
  - ii. **Serious adverse events**

- iii. Episodes of ventricular tachycardia or fibrillation
- iv. Episodes of syncope
- v. Episodes of seizure
- vi. Adverse events resulting in the subject discontinuing from the study.

- Submission of the related ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
- A completed Highlights of Clinical Pharmacology Table (Table 1, shown below)

**Note: please submit all data sets in CDISC SDTM format if possible.**

**Table 1. Highlights of Clinical Pharmacology**

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)

Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.
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Nonclinical Questions:

Structure of eCTD Module 4 (Nonclinical)

*The Gadobutrol NDA will be prepared in eCTD format. More than 100 pharmacology and toxicology reports have been submitted to IND 56,410. Many of these reports were submitted as part of the initial submission (Serial No. 000, submitted 15 July 1998) to support clinical trials of a 0.5 M formulation, or submitted electronically as a CD-ROM (Serial No. 013, December 30, 2003) at the time of reactivation of this IND for study of the new 1.0 M (1.0 mmol Gd/mL) formulation. In order to fully populate the nonclinical part of eCTD backbone, all available nonclinical reports were submitted electronically in eCTD format in an Information Amendment to the IND on December 23, 2009 (SN 203). It is intended that the integrated nonclinical overview summary presented in this Pre-NDA meeting briefing package will be used as the Nonclinical Overview of the NDA eCTD (Module 2.4). The Nonclinical documents to be contained in the NDA will consist of this Nonclinical Overview (Module 2.4) and tabular overviews listing all pharmacology, pharmacokinetics, and toxicology reports in Modules 2.6.3.01 (pharmacology), 2.6.5.01 (pharmacokinetics), and 2.6.7.01 (toxicology), with cross-references (without hyperlinks) from these NDA documents to the location of reports in the IND Information Amendment. Textual summaries for Pharmacology (Module 2.6.2), Pharmacokinetics (Module 2.6.4) and Toxicology (Module 2.6.6) will not be submitted to the NDA.*

*Sponsor's Question 5a:*

*Does the Agency agree that the overall format and contents of the integrated nonclinical overview summary as presented in this Pre-NDA meeting briefing package, along with the tabular overview summaries for all studies (see Table 7-1, Table 7-2, and Table 7-3 of Appendix 5), are acceptable for filing?*

**FDA's Response 5a:**

**No. While, the overall content of the nonclinical overview summary appears acceptable for filing, we do not agree with the proposed format especially with the proposal to cross reference (without hyperlink) from the NDA documents to the location of the reports in the IND). Please see our response to question 5b on the need for the P/T portion of the NDA to be self-sufficient and able to stand entirely on its own without the need to refer to the IND. We expect hyperlinks and cross references within the NDA.**

*Sponsor' Question 5b:*

*Bayer proposes to submit all nonclinical study reports to the IND, with inter-application (NDA - IND) cross-references (without hyperlinks) from the NDA nonclinical overview summary and tabular overviews to these reports. Does the Agency agree that Bayer does not need to resubmit all nonclinical study reports to the NDA?*

**FDA's Response 5b:**

**No.**

(b) (4)

*GLP Status of Safety Pharmacology Studies*

*Gadobutrol was formulated for intravenous use in 2 concentrations, 0.5 mmol/mL (SH L562 A) and 1.0 mmol/mL (SH L562 B and SH L562 BB). SH L562 B refers to drug substance being produced in early development stages with a slightly different process (b) (4) SH L562 BB refers to drug substance being produced as submitted within the NDA. Pivotal safety pharmacology studies of SH L562 BB (1.0 mmol Gd/mL) (effects on electroshock-induced convulsions in mice, cardiovascular effects in conscious telemetered dogs, and effects on respiratory function in anesthetized rabbits) were conducted according to GLP regulations in accordance with ICH Guidelines S7A and S7B. However, several other safety pharmacology studies of the effects of Gadobutrol were conducted before official implementation of the ICH S7A guideline in 2001. These studies were conducted according the state of the art at the time of performance, but not according to GLP standards. These included studies of CNS function (Irwin test), effects on hERG-mediated potassium current in CHO cells, cardio-hemodynamic function in anesthetized dogs, respiratory function in rabbits, renal function in rats, bleeding time in rats, erythrocyte morphology, and in vitro histamine release. An overview of the Safety Pharmacology program for Gadobutrol can be found in Section 2 of the Integrated Nonclinical Overview Summary (Appendix 5), and a list of safety pharmacology studies and the GLP status of each study can be found in Table 7-1 of Appendix 5.*

*Sponsor's Question 6a:*

*Does the Agency concur that*

(b) (4)

(b) (4)

**FDA's Response 6a:**

No.

(b) (4)

*Sponsor's Question 6b:*

*Furthermore, does the Agency concur that the safety pharmacology testing program of SH L562 BB described above is sufficient to support the submission of an NDA for Gadobutrol?*

**FDA's Response 6b:**

**The safety pharmacology studies for testing SH L562 BB and described in the information package appear sufficient to support filing of the Gadobutrol NDA. However, the adequacy of these studies is a review issue.**

Toxicology Studies

*The pivotal GLP toxicology studies conducted using the to-be-marketed SH L562 BB (1.0 mmol Gd/mL) formulation included:*

*Expanded, single intravenous dose systemic toxicology studies in rats and Beagle dogs (Reports A28309, A41318)*

*- 4-week (7 days/week) intravenous systemic toxicology studies in rats and dogs with post-dose recovery periods of 10 weeks (rats) and 8 weeks (dogs) for controls and high-dose animals (Reports 9658, A10548)*

*Reproduction toxicology studies exploring fertility and early embryonic development in rats, embryo-fetal development in rats and in rabbits, and perinatal and postnatal development including maternal function in rats (Reports A39049, A34150, A36661, PH-35738)*

*A discussion of the results of these studies can be found in Section 4 of Appendix 5, and Table 7-3 contains a listing of these studies and cross-references to the location of these reports in previous submissions to IND 56,410.*

*Sponsor's Question 7:*

*Does the Agency concur that the above mentioned pivotal intravenous systemic and reproduction toxicology studies of SH L562 BB, in addition to an extensive series of supportive studies conducted using the developmental SH L562A/AA (0.5 mmol Gd/mL)*

*formulation, are acceptable with respect to scope, general design, and duration for submission of an NDA for Gadobutrol?*

**FDA's Response 7:**

**Yes. However, please provide sufficient clarity on the comparability of the developmental SH L562A/AA (0.5 mmol Gd/mL) formulation and the to-be-marketed formulation SH L562 BB (1.0 mmol Gd/mL) in order to determine the adequacy of studies conducted with the SH L562A/AA formulation for NDA submission.**

*Genotoxicity Studies*

*Studies of the genotoxicity of Gadobutrol were conducted using the developmental SH L562A/AA (0.5 mmol Gd/mL) drug product formulation. The results of these in vitro studies (Ames test, HGPRT/V79 mutation test, chromosomal aberration tests in human lymphocytes) and the in vivo mouse micronucleus test are considered relevant for assessment of the genotoxicity of the Gadobutrol test substance.*

*A discussion of the results of these studies can be found in Section 4 of Appendix 5, and Table 7-3 contains a listing of these studies and cross-references to the location of these reports in previous submissions to IND 56,410.*

*Sponsor's Question 8:*

*Does the Agency concur that genotoxicity studies conducted using the developmental SH L562A/AA formulation will be acceptable for submission in the NDA in lieu of similar studies conducted using the SH L562 BB final marketed drug product?*

**FDA's Response 8:**

**Yes. Genotoxicity studies conducted using the SH L562A/AA formulation are acceptable for submission in the NDA.**

*Carcinogenicity Studies*

*Gadobutrol Injection is intended to be applied in a single diagnostic dose to humans. Gadobutrol is not metabolized in animals or in humans, and the intact complex is quickly eliminated from the body, and there is no evidence of accumulation in tissues after repeated administration. Gadobutrol is not mutagenic and no pre-neoplastic lesions were observed in repeat-dose toxicity studies in rats and dogs. Therefore, there is no cause for concern regarding carcinogenicity of Gadobutrol and carcinogenicity studies are not planned. Based on criteria used to determine the need for a carcinogenicity study (as specified in the ICH S1A guidance), Bayer believes that a waiver for carcinogenicity studies of Gadobutrol is warranted.*

*Sponsor's Question 9:*

*Does the Agency concur that a waiver for carcinogenicity studies with Gadobutrol is appropriate?*

**FDA's Response 9:**

**Yes, please submit a waiver request with justification in your NDA.**

*Calcobutrol as an Excipient*

*A single-dose intravenous toxicity study was conducted in male and female mice to compare acute toxicity of calcobutrol (5 and 25 mmol Gd/kg), used as an excess complexing agent in the SH L562BB formulation, with that of the developmental SH L562 AA (0.5 mmol Gd/mL) formulation, and that of Gadobutrol (25 mmol Gd/kg). In this study, the maximum lethal dose (MLD) for calcobutrol sodium (25 mmol Gd/kg) in both males and females was the same as the MLD for Gadobutrol. The maximal non-lethal dose of calcobutrol (5 mmol Gd/kg) after single intravenous administration in mice corresponded to 50,000 times the systemic burden after the estimated clinical dose (1 µmol/kg) of the excipient, in terms of body weight. A further discussion of the results of this study can be found in Section 4 of Appendix 5. The report for this study (Report SG/130) was submitted in an Information Amendment to IND 56,410 on December 23, 2009 (SN 203).*

*Sponsor's Question 10:*

*Does the Agency concur that the study described above would be sufficient to toxicologically qualify calcobutrol sodium (CaNa-butrol) as an excipient for use in the Gadobutrol (1.0 mmol Gd/mL) drug product?*

**FDA's Response 10:**

**We are unable to provide a response at this time as this is a review issue.**

*Chemistry, Manufacturing, and Controls Question*



(b) (4)

*Sponsor's Question 11:*

(b) (4)

**FDA's Response 11:**

(b) (4)

. However, see the specific Product Quality Microbiology response below.

**We also note that you plan to include a Pharmacy Bulk Pack in the same application with the other presentations. However, there is no discussion in the briefing package regarding the stability of the proposed Pharmacy Bulk Pack. Be advised, that the Pharmacy Bulk Pack and vials should be submitted under separate NDAs. Pharmacy Bulk Packs are manipulated and have a different delivery system, and therefore require specific labeling.**

**Product Quality Microbiology**

**Specific labeling will be required for the Pharmacy Bulk Pack in the proposed 30mL and 60mL configurations. This labeling will be distinct from the vial label.**

(b) (4)

**conditions. Reference is made to *Guidance for Industry: ICH Q8 Pharmaceutical Development*, Section II.E and *Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products*, Section 2.2.7. <http://www.ich.org/cache/compo/276-254-1.html>.**

**The study report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product constitution. It is generally accepted that growth is evident when the population increases more than 0.5 Log<sub>10</sub>. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature.**

We note that identical bulk solution will be filled into various sizes and (b) (4)  
Since no further information was provided, we bring your attention to the Sterilization Validation information that should be submitted in the NDA application which should include (and is not limited to) the following:

- Identification and Characterization of bioburden at the bulk manufacturing stage.
- Process Validation and/or Evaluation of the (b) (4) process.
- Environmental monitoring program (action levels and methods).
- Container-closure integrity studies for each container-closure system that will be used in commercial production.
- Method suitability studies for the sterility and bacterial endotoxins tests.

The sponsor is also reminded to refer to the following guidance when submitting the NDA application: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, Final 11/1994 and MAPP 5040.1 for CTD format.

#### Regulatory Questions

#### Applicant Orientation Meeting

Sponsor's Question 12:

*Does the Agency anticipate requesting an Applicant Orientation meeting for the Gadobutrol NDA?*

**FDA's Response 12:**

**Yes. It is anticipated that the applicant will be asked to present an overview of the product development program at an orientation briefing. The briefing usually occurs within three months of submission of the NDA.**

#### Proprietary Name Submission for Gadobutrol

*Bayer intends to submit a Request for Proprietary Name Review to the IND for the evaluation of "Gadovist® 1.0" as the proposed proprietary name for Gadobutrol injection.*

Sponsor's Question 13:

*Does the Agency have any comments on our plans to submit "Gadovist® 1.0" as the proposed proprietary name for Gadobutrol?*

### **FDA's Response 13:**

**Yes. You must submit a request for the evaluation of the Proprietary Name either as an amendment to your NDA or as a separate amendment to your IND. You should refer to the "Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names" for additional guidance on the contents of the amendment. Your request for review of the product's Proprietary Name must be prominently displayed in your cover letter. The review of the Proprietary Name cannot begin until the submission of this amendment. The amendment must contain all of the elements cited in the Guidance. You should include proposed labeling (Carton & Container) with this submission as well. This should be done as soon as possible.**

### *Other Potential Review Issues*

#### *Sponsor's Question 14:*

*After review of the briefing package, has the Agency identified any review issues that may affect the filing or review of the NDA?*

### **FDA's Response 14:**

**It is premature to address the filing of the application at this time. The filing of the application is based on the presence or absence of specific components of the application at the time of submission and their completeness. It is premature to address any review issues since the application has not been submitted.**

### **Discussion**

Bayer Healthcare asked that we focus on questions 1, 2, 4, 5, and 11 during the meeting. Bayer expressed that they had no additional questions or responses to the other questions and responses provided to them by FDA. Bayer then stated their plan to provide financial disclosure information for studies 310123 and 310124. Bayer considers them pivotal efficacy studies and the data will be pooled. Bayer also stated that the Japanese data would be removed and not included in the Integrated Summary of Efficacy (ISE). According to Bayer, the Japanese data would be added to the pooled data submitted as supportive data not as part of the data submitted for primary analysis in support of the proposed indication. Study 310164 would not be included in the ISE. According to Bayer, this was a change in background for question 1 and was included in the meeting request but excluded from the meeting package.

Regarding question 2, Bayer stated that all subjects who received Gadovist during the clinical investigation would be included in the Integrated Summary of Safety (ISS). FDA then asked why subjects from the Phase 1 trials were not included in the Integrated

Summary of Efficacy (ISE) for the product. Bayer replied that subjects included in the Phase 1 studies were mainly healthy volunteers and that was the reason for their exclusion from the ISE. Bayer said that the methodology used for the efficacy analysis would be clarified in their NDA submission and one Phase 2 study of the 0.1mmol/kg dose would also be included in the Integrated Summary of Efficacy (ISE).

Bayer stated the clinical pharmacology data would be submitted in an electronic format, but the data format including QT data would not be in the CDISC format. FDA stated that they would let the sponsor know about the acceptability of submitting the QT data in a format other than the CDISC format after getting input from the IRT-QT team. (Please note that the IRT-QT team is accepting other electronic data format, e.g., SAS transport format, while CDISC is desirable.)

Regarding question 5, Bayer stated that all non-clinical study reports would be submitted to the NDA, and hyperlinks to the data from the IND would also be included in the NDA non clinical section. All nonclinical summaries will be submitted. Sections 2.4, 4.1 will be submitted but section 2.6 will not be submitted.

Bayer HealthCare stated that they have stability data for the Pharmacy Bulk Package that will be part of the submission for Gadovist. According to Bayer the information was not submitted because they only provided summaries of their plan for the NDA submission. Bayer again queried FDA on the submission of two NDAs for Gadovist (one for the vials and one for the Pharmacy Bulk Pack). FDA reiterated its previous recommendation that each application should be submitted as a separate entity. However, FDA also stated that it would reconsider this advice and provide a decision to Bayer on the need to submit two NDAs for the product rather than one. FDA conveyed to Bayer that if there was a problem with one of the applications and they were submitted as one that both NDAs would potentially receive a Complete Response Letter (CR) even if the conditions for issue of the CR letter was only applicable to one of them. Bayer said that this was understood and asked how soon FDA would get back to them regarding this issue. FDA replied that they would respond as soon as possible.

## **Summary**

Bayer agreed with the responses provided to them by FDA in the FDA meeting response of February 2, 2010. However, Bayer requested clarification and queried FDA about the following questions: 1, 2, 4, 5, and 11. Bayer stated that they planned to submit their NDA in May, 2010. FDA stated that with regard to question 11 and whether separate NDAs for the Pharmacy Bulk Package and the vials were needed, FDA would confer internally and provide a decision to Bayer on whether it was necessary to submit two NDAs or one for the two presentations of the product.

The minutes were prepared by James Moore, Project Manager.

James Moore, PharmD., M.A.  
Project Manager, DMIHP

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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IND-56410

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GI-1

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BERLEX  
LABORATORIES  
INC

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GADOBUTROL INJECTION

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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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JAMES W MOORE  
04/26/2010



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** October 12, 2007

<b>To:</b> Sibylle Jennings	<b>From:</b> James Moore
<b>Company:</b> Bayer Healthcare Pharmaceuticals	Division of Medical Imaging and Hematology Products
<b>Fax number:</b> 973-487-2016	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> 973-487-2027	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Fax of Meeting Minutes, I56,410 (Gadobutrol), Industry Meeting August 28, 2007	

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**Total no. of pages including cover:** 12

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**Comments:**

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**Document to be mailed:**             YES             NO

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Industry Meeting between the Division of Medical Imaging and Hematology and Bayer HealthCare, Tuesday August 28, 2007, 12:30PM-2:00 PM, FDA White Oak Campus, Building 22, Room 1313

Subject: IND 56,410 Gadobutrol (Gadovist)

Bayer HealthCare Attendees:

Sibylle Jennings, Ph.D., Associate Director, Global Regulatory Affairs  
Thomas Balzer, M.D., Ph.D., Vice President, Head Global Clinical Development  
Diagnostic Imaging  
Christine Becker, M.D., Senior Director, Head Global Regulatory Affairs Diagnostic  
Imaging  
Josy Breuer, M.D., Ph.D., Executive Director, Global Clinical Development Diagnostic  
Imaging  
Suming Chang, Ph.D., Director, Statistics  
Juan Guitierrez, M.D., Director, Global Clinical Development Diagnostic Imaging  
Robert Hehr, Ph.D., Senior Clinical Statistician  
Louis Mylecraine, Ph.D., Director, Nonclinical Development  
Martin Rosenberg, M.D., Executive Director, Global Clinical Development Diagnostic  
Imaging  
Marcus Schultze-Mosgau, Ph.D., Director, Clinical Pharmacology

FDA Attendees:

Rafel Rieves, M.D., Acting Division Director, DMIHP  
Barbara Stinson, D.O., Clinical Reviewer, DMIHP  
Alex Gorovets, M.D., Clinical Team Leader, DMIHP  
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP  
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, OCP  
Anthony Mucci, Ph.D., Statistical Reviewer, OB  
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB  
Tushar Kokate, Ph.D., Pharmacology/Toxicology Reviewer, DMIHP  
James Moore, PharmD., M.A., Project Manager, DMIHP

## **Background**

Bayer HealthCare requested this meeting in a meeting request dated July 2, 2007. FDA provided a response to the meeting package prior to the meeting. Here are FDA's preliminary responses provided to Bayer HealthCare in the fax on August 27, 2007.

In reference to your IND 56,410 for Gadovist (Gadobutrol), Serial 037 (the meeting package dated July 25, 2007), we have reviewed the submission in preparation for the meeting scheduled for August 28, 2007. FDA's preliminary responses to the sponsor's questions are presented below and are followed by additional comments.

Please note that the reliance on the imaging variables for establishing the diagnostic effectiveness of your product and their relation to the efficacy claim you appear to propose continue to be of concern to us. We are obtaining an internal Neurology consult to help us address some of these issues and this in turn might have bearing on the future review process.

**Question 1:** The clinical diagnosis established by the investigator and/or treating physician will be considered final following evaluation of findings from referral through a 3-month follow-up period (excluding the study Gadovist®-enhanced MRI), after the last study-related MRI procedure. This may include additional imaging procedures, relevant clinical laboratory data, histopathology, symptomatology (better, worse, same, or new), and other available relevant information deemed necessary by the investigator and/or treating physician. A 3-month follow-up was chosen because it is consistent with current clinical practice for the target population and is considered to be sufficient to establish a final clinical diagnosis. The final diagnosis will be compared to the diagnoses of the investigator/blinded reader for each of the 3 image sets as a secondary variable and will also be used to determine normal and abnormal brain tissue. In order to provide the most reliable and robust standard, all available patient related information leading to his/her referral for contrast MR will be collected (including but not limited to comparative imaging tests, laboratory results, histopathology results, neurological examinations, and current pharmacotherapy).

Is the method of establishing the standard of truth as described in clinical study protocols 310123 and 310124 under section 8.2.2.2.5 (see section 10.1/10.2) including the implementation of a clinical follow-up of up to three months acceptable to the Division?

**Division Preliminary Response:** *The general description of the standard of truth is conceptually acceptable.*

*However, please provide justification for the choice of 3 months as time for follow-up. (The Division is also in the process of seeking a Neurology consult on this issue).*

*Please also clarify that a clinical investigator providing the Standard of Truth assessment will be blinded to all study MRI images and interpretations (not just Gadovist-enhanced images) and describe in detail how this blind would be maintained.*

**Question 2:** A review of the study data from the completed US Phase 2 study, which included a comprehensive 72-hour follow-up, revealed that the vast majority of adverse effects were seen within 24 hours (see section 9 of Summary of results of clinical Phase 2 study #308200), which is in line with controlled safety data obtained in clinical studies worldwide in more than 3000 patients (see 12.1 adverse drug reactions (ADRs) in clinical trials and from spontaneous post marketing reporting according to Gadovist® Reference Safety Information.) The sponsor therefore proposes the following safety follow-up evaluations in the pivotal phase 3 studies:

- In the crossover comparison study (protocol #310123) which utilized Prohance® as a comparator, a complete 24 hour safety follow-up (serum chemistry, hematology, urinalysis, physical exam, vital signs, AE monitoring) will be performed after administration of Gadovist® and Prohance®
- In the non-comparison study (protocol 310124), we propose, in addition to the complete 24 hour safety follow-up, an additional 72 hour telephone follow-up for collection of Adverse Events

Does the Division agree that the proposed safety evaluation for the Phase 3 program (see also clinical study protocol 310123 and 310124 (see section 10.1/10.2) is adequate?

**Division Preliminary Response:** *No. The Division recommends that the patient population that will be studied should include patients with moderate renal insufficiency. As such, a more complete safety follow-up needs to be obtained at 72 hours. In addition, we note that since contrast injections will be separated by a 24 hour time frame, this time frame will need to be increased accordingly (at least to 72 hours).*

**Question 3:** After careful consideration of physico-chemical properties and safety profiles of all approved extracellular gadolinium based contrast agents we propose to use Prohance® as the active comparator in protocol #310123. Prohance® was selected considering the issue of NSF and the fact that macro-cyclic Gd-based contrast agents (GBCA) such as Prohance® and Gadovist® have a substantially higher stability than linear GBCA and may provide an additional margin of safety.

Does the Division accept the selection of Prohance as the comparative agent?

**Division Preliminary Response:** *Please see Additional Comments below in reference to the methods of contrast injection and the validity of the four efficacy variables as applicable to Prohance. Recognizing that the Multihance label cites the clinical studies that utilize the efficacy variables similar to the ones you propose for your studies, please comment on the reasons for not selecting Multihance as the comparator.*

*Please provide a brief comment on the physico-chemical properties, including relaxivity, of different comparator candidates you have considered.*

*We recommend that the choice of a comparator, if possible, provides for comparison between the drugs not confounded by the differences in methods of administration, that the performance of comparator is not affected by administration of a dose of a drug insufficient to achieve adequate imaging, and that the amount of the administered comparator needed to achieve an adequate image is safe in the setting of the trial design.*

(b) (4)

**Division Preliminary Response:** *No.*

**Question 5:** Three independent blinded readers will evaluate the four visualization parameters that are being proposed for use in studies 310123 and 310124: degree of contrast enhancement, border delineation, internal morphology, and total number of lesions. We propose the following image sets in a masked/blinded reading to be presented in multiple sessions:

COMPARISON STUDY #310123

- Unenhanced MR Image Set: T1W, T2W, FLAIR
- Combined Unenhanced + Gadovist® Enhanced MR Image Set: T1W enhanced + T1W, T2W, FLAIR
- Combined Unenhanced + Prohance® Enhanced MR Image Set: T1W enhanced + T1W, T2W, FLAIR

NON-COMPARISON STUDY #310124

- Unenhanced MR Image Set: T1W, T2W, FLAIR
- Combined Unenhanced + Gadovist® Enhanced MR Image Set: T1W enhanced + T1W, T2W, FLAIR

For the primary efficacy analysis, the unenhanced image set and the combined unenhanced and enhanced image set(s) for each patient will be randomized and presented to the readers in sessions separated by at least one week.

Is the Sponsor's proposed plan for the blinded evaluation of the primary visualization parameters acceptable?

**Division Preliminary Response:** *The proposed sequences might be acceptable but require a more detailed explanation. Please justify the choice for the one week time interval between reading sessions. In addition, please note that the time interval should be pre-specified for both protocols and for the image set categories (enhanced, un-enhanced etc) that comprise the protocols.*

**Question 6:** The blinded readers will assess the following additional secondary endpoints, which have been incorporated in the Phase 3 study protocols consistent with the discussion and written comments from the Type C Meeting on 24 May 2007:

1. In the comparative trial-non-inferiority for the exact diagnosis Gadovist® versus Prohance® for the respective combined unenhanced and enhanced image sets.
2. For the non-comparative trial, improvement in exact match diagnosis for the unenhanced image set vs. combined unenhanced + Gadovist® enhanced image sets.
3. Improvement in sensitivity and specificity for the normal/abnormal based on the comparison of the T1W Gadovist®/Prohance® enhanced and T1W unenhanced MR images.

Does the Division agree to these proposed additional secondary endpoints for the assessment of disease (normal/abnormal)?

**Division Preliminary Response:** *For the non-comparative trial (#2), the combined unenhanced + Gadovist® enhanced image sets should show improvement in the exact match diagnosis compared to the unenhanced image set. #1 and #3 as stated in the question are acceptable. To further improve the clinical meaningfulness of the data and as a measure of the clinical utility of the studies, please conduct a subset analysis to evaluate performance characteristics of the Test methodology for detection of malignant neoplasms.*

**Question 7:** For the primary endpoints, the four visualization parameters used in the US Phase 2 study 308200 will also be evaluated in the Phase 3 study, but no composite score will be calculated. Each of the four parameters will be evaluated individually by both the Clinical Investigators at the study sites and subsequently by 3 Blinded Readers. Three variables will be analyzed separately for superiority (internal morphology, border delineation and degree of enhancement) and noninferiority will be assessed for one variable (number of lesions) to unenhanced MRI for both studies and also for noninferiority to Prohance® in the comparison study. They will be treated strictly as ordinal variables with higher scores indicating better performance. The average score for the three readers will be analyzed in addition to the scores from the three individual readers. The primary analysis will be done on these average scores.

Does the Division find this approach to the analysis of the primary endpoints acceptable?

**Division Preliminary Response:** *Pending more detailed comments from our Statistics Reviewer on the statistical aspects of the proposal, the proposed analyses appear to be acceptable.*

*Of note, the gadoteridol package insert does not refer to the evaluation of any of the 4 proposed variables during the clinical trials of gadoteridol, and you have previously stated (response to FDA fax of 22 May 2007) that "For these particular variables, no standard of truth will be used."*

*Please clarify the role, if any, of the clinical investigators in the assessment of the primary endpoint variables as you seem to indicate in your question above.*

**Question 8:** We intend to include some of our Phase 2 investigators/sites, among all of the sites in our 2 pivotal Phase 3 trials.

Is it acceptable to include some of the Phase 2 study investigators/sites in the Phase 3 program?

**Division Preliminary Response:** *Due to possible introduction of bias, it would be a review issue. In addition, it might affect the variability in the standard of truth assessment.*

**Question 9:** A “Multi-center, Open-Label, Controlled Study for Evaluation of Pharmacokinetics, Safety and Tolerability of a Single Dose of 0.1 mmol/kg BW Gadovist® 1.0 in Children aged 2 to 17 years” is currently ongoing in Europe with 140 subjects to be enrolled. This study is conducted in compliance with ICH E11, the Guidance for Industry “How to comply with the Pediatric Research Guidance for Industry “General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products” (November 1998). It is our understanding that FDA accepts pediatric data from foreign studies in order to avoid repetition of studies in children. The Sponsor, therefore, plans to submit the data from the pediatric study 310788 that is ongoing in Europe and Canada (please see 11.1 for outline of the study protocol and 11.2 for the full study protocol) to comply with the request for pediatric assessment for a new drug.

Does the Division agree that in the case of Gadovist®, effectiveness can be extrapolated from safety and PK data in children according to ICH 11 and the Guidance for industry “How to comply with the Pediatric Research Equity Act” (September 2005)?

**Division Preliminary Response:** *This is acceptable.*

**Question 10:** As outlined in section 11.1 and 11.2, pediatric study 310788 that is ongoing in Europe and Canada will include patients aged 2-17 years. The age group 0-2 year old children was not included due to general ethical concerns. This age group is generally the most vulnerable population in any clinical study. The requirement associated with a clinical study such as the necessity to obtain multiple blood samples represents a greater burden for the 0-2 year olds compared to older children. A pediatric development plan for Gadovist® is included in this package under section 11.3. In general Bayer follows a step-wise development approach for Gadovist® by first gaining sufficient experience about the safety profile in adults followed by an evaluation in a pediatric population with a relatively high incidence of contrast-enhanced MRI procedures and with mostly completed organ and organ function development comparable to that of an adult population, i.e. in children and adolescents 2-17 years. Bayer is currently evaluating the usefulness and possibility of conducting a clinical study in the age group 0-2 years. Based on the results of study 310788 as well as ethical

considerations Bayer will make an assessment whether general pediatric effectiveness and safety can be expected for patients in this particular age group.

Does the agency concur, that due to the limited knowledge currently available, it is adequate to discuss the necessity and appropriateness of conducting clinical trials in the specific pediatric population of 0-2 years after having the results of the ongoing clinical trial (study 310788)?

**Division Preliminary Response:** *The Division notes the clinical relevance and utility of studies in the 0-2 age group, however the Division also concurs that it is safer to defer studies in this age group at this time.*

**Additional Comments to the Sponsor:**

1. *We note that Gadobutrol and gadoteridol (Prohance), the proposed comparator drug, will be administered as an IV single dose and we further note that gadoteridol will be administered as an IV infusion whereas Gadobutrol will be administered by power injector at a constant rate.*

*Since contrast materials have restrictions in flow rates, please clarify whether Gadobutrol has been studied/approved for delivery by this method.*

*Please also comment on any anticipated effect on efficacy parameters that might occur by not standardizing the method of drug delivery between the Test and the Comparator.*

*In addition, the Prohance label allows the administration by either rapid infusion or by bolus. Please clarify which method your investigators will be using and why, from the standpoint of safety and efficacy.*

*Furthermore, Prohance label allows a follow-up double-dose "in patients suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans." These provisions call into question the appropriateness of choosing Prohance as a Comparator and make it a review issue as a result.*

2. *You have proposed the use of gadoteridol as a comparator and note evaluation of 4 primary efficacy variables, (total number of lesions detected, assessment of border delineation, degree of contrast enhancement, and internal morphology of lesions), for each drug. You further note that for each of the 4 variables, the non-inferiority of Gadobutrol versus gadoteridol will be evaluated. However, the gadoteridol package insert does not note the evaluation of any of these 4 variables during the clinical trials of this product.*

*This is problematic, and we recommend that you perform appropriate sensitivity*

*analyses demonstrating the superiority of Prohance-enhanced and un-enhanced images over un-enhanced in the setting of your trial.*

3. *Please clarify how efficacy parameters used to evaluate the normal structures will be used in the analysis of endpoints and note how you propose to show that the comparator Prohance® enhanced scans are ‘better’ than unenhanced scans for normal structures and for the 4 efficacy variables.*
4. *As discussed previously, we recommend pre-specifying the acceptable level of performance on an un-enhanced scan. Comparator performance, whether a drug comparator or an image comparator, will be a review issue.*
5. *The current submission (serial number 37) does not include an investigator’s brochure or blinded reader manual however it is noted that the efficacy variables will be evaluated both by the on site investigator and three blinded readers. We have the following comments concerning the blinded reads:*
  - *Please clarify the role of the on site investigator and note whether the same 3 readers will be used to evaluate all patients in both studies as well as provisions for study readings in case a reader is unable to complete his/her workload.*
  - *In addition, since it is noted that each of the three blinded readers will independently evaluate 3 out of the 4 efficacy parameters (variables) for superiority and the 4<sup>th</sup> variable, number of lesions, for non-inferiority, please address how this will be handled in the statistical analysis plan.*
  - *Please address the issue of inherent reader bias with regards to the superiority of contrast images to non-contrast image that may occur if a single reader is used for interpretation of both unenhanced and enhanced images.*
  - *Please address the handling of uninterpretable images.*
6. *Your protocols call for continued enrollment until a pre-specified number of patients is achieved. Please document all drop-outs and the reasons for dropping out before the number is achieved, and specifically whether any imaging had been performed prior to dropping out.*
7. *The proposed indication as taken from section 3 of the submission gives both functional and anatomic indications and notes specific disease processes and elsewhere in the submission is stated differently. Please clarify the proposed indication. The Division has submitted a consult to Neurology addressing the relation of the efficacy parameters to the indication(s) statement.*
8. *The two proposed trials will be performed in different geographical regions. We recommend that you standardize the image acquisition methodology among the participating sites and provide the FDA with an image acquisition manual for review.*

9. *We have the following additional comments concerning determination of the “truth standard” for assessment of sensitivity and specificity:*

*The Phase 2 study was designed to perform both a lesion tracking process to correlate position of lesions in the brain and a comparison of the MR imaging results to histopathologic and other clinical results.*

*Please comment on the findings based on the Phase-2 study.*

*Please note the reason that this will not be continued for the Phase 3 study.*

10. *Please provide a list of all pre-clinical studies that were conducted (and ongoing) under the IND with a comprehensive written and tabulated summary with key findings and NOAELs.*

## **Discussion**

At the beginning of the meeting Bayer HealthCare presented the results from their completed Phase 2 study. Bayer HealthCare asked the Division to provide further discussion of responses to their questions 1, 2, 3, 4, 7, 8 and of additional comments 4, 7 and 10 (see above).

FDA queried Bayer HealthCare on the reason for their timeline of 3 months for follow-up of patients in the trial. Bayer HealthCare responded that this is acceptable clinical practice for this group of patients. Bayer also stated that most inflammatory diseases resolve in 3 months. FDA also asked Bayer about patients who die prior to the 3 month assessment period and Bayer responded that all the data for all patients would be included in the follow-up of the patients in the study and that it was possible to obtain histopathology data on patients who die prior to the 3 month follow-up period. FDA stated that based on the points made by Bayer HealthCare the 3 month follow-up period seemed reasonable. Bayer HealthCare stated that a written response would be provided to FDA in 2 weeks that would provide additional detail on follow-up of these patients.

FDA also queried Bayer HealthCare about the proposed indication for the product and Bayer HealthCare responded that the indication has changed and the information as provided in the meeting package where the indication was described contained information in parenthesis that was an example for information purposes. According to Bayer HealthCare the claim presented for Gadovist will be a (b) (4)

FDA queried Bayer HealthCare about the standard of truth for the trial and asked which investigator would be responsible for assessing the standard of truth. After much discussion Bayer stated that the referring physician was the clinician that would be responsible for establishing the standard of truth through clinical assessment. When asked whether the clinician would have access to the images Pre or Post, Bayer HealthCare responded that the clinician may see some images to assist in diagnosis, but

the images that will be seen by the investigator will not be images taken from the Gadovist trial.

FDA then asked if the comparator (Prohance) will be delivered at the same rate and the same manner to all subjects in the trial. Bayer HealthCare responded that the manner of delivery of Prohance and Gadovist will be the same.

FDA requested that Bayer HealthCare clarify the roles of the adjudicator, blinded readers, and investigators in their proposed submission because the meeting package did not clarify or adequately describe each of their roles. Bayer HealthCare said that the respective roles would be clarified in the upcoming submission.

FDA suggested to Bayer HealthCare that they should consider use of a clinical panel to establish the standard of truth for the trial. FDA suggested use of at least 2 clinicians and an adjudicator when needed if the panelists cannot agree on the diagnosis. Use of the panel according to FDA would make the standard of truth finding more robust.

FDA asked Bayer about the wording of the indication and told Bayer HealthCare that the indication was unclear in the meeting package. Bayer HealthCare said that the indication would be clarified in the response that would be provided to FDA in two weeks.

Regarding the safety of Gadovist in renally impaired patients, Bayer HealthCare acknowledged their plan to exclude patients with renal impairment from their Phase 3 study because of the safety of the product in these patients and the potential for development of Nephrogenic System Fibrosis (NSF). FDA responded that they should not exclude these patients from the trial because important safety information could be gathered from these patients. Bayer HealthCare responded that the difficulty would be convincing an IRB that the drug should be studied in this patient population. Bayer also stated that Prohance would not be studied in either moderate or severe renally impaired patients. FDA suggested that Bayer HealthCare reconsider including patients with moderate and severe renal impairment in the trial. Bayer said they would reconsider their decision of whether to include moderate/severe renally impaired patients in their trial. Regarding monitoring of renal function, FDA recommended that Bayer HealthCare collect serum creatinine values at baseline, before dosing with the second agent and at 24, 72, or 96 hours post injection (Bayer HealthCare had proposed collecting values for the serum creatinine at the 72 hour timepoint only).

Bayer HealthCare stated that they had data on renally impaired patients treated with Gadovist from a Phase 1 trial. FDA asked that the information from the trial be included in the submission that would be sent in the next 2 weeks. Bayer Health Care agreed to provide that information.

FDA queried Bayer HealthCare on the use of the comparator Prohance. FDA asked Bayer HealthCare why Prohance was chosen. Bayer HealthCare responded that because of the macrocyclic structure of Prohance there have been fewer cases of Nephrogenic System Fibrosis (NSF) seen with this agent than other gadolinium based contrast agents

and that was the reason for its selection. FDA replied that Prohance is approved for a different indication than is proposed for Gadovist and although there might be safety advantages with Prohance the latter might be an under-performing comparator when studied for the proposed indication. Bayer HealthCare also stated that they had done bridging studies in Japan using Prohance and that these studies demonstrated that Prohance had a better safety profile than other gadolinium agents.

FDA inquired of Bayer HealthCare whether they planned to ask for a comparative efficacy claim since Prohance was being used in the trial. Bayer HealthCare replied that they did not plan to seek a comparative efficacy claim.

According to Bayer HealthCare there will be three sets of analyses performed in the trial. Gadovist combined pre-post images, unenhanced alone, and the enhanced alone. There will be a similar analysis performed for Prohance. The design of the Phase 3 trial will be the non-inferiority model. There will be three blinded readers for the trial with an adjudicator to assess lesions if the number of lesions found by a reader differs from the other readers. According to Bayer HealthCare the adjudicator will not seek to describe the variability of interpretation of lesions among readers.

According to Bayer, some of the same readers used in the Phase 2 study may be used in the Phase 3 study and FDA said that they preferred that the readers were different but would accept this design if Bayer HealthCare decides to use it. FDA did express concern that this could introduce some bias into the study.

### **Summary**

Bayer HealthCare will provide a full response to the Division's August 27, 2007 response to Bayer HealthCare's meeting package. Bayer will also revise its indication statement and the program for safety monitoring in the trial.

The minutes were prepared by James Moore, Project Manager.

James Moore, PharmD., M.A.  
Project Manager, DMIHP

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James Moore  
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