

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 22-090**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22,090

SUPPL #

HFD # 160

Trade Name Eovist

Generic Name Gadoxetate Disodium

Applicant Name Bayer Healthcare Pharmaceuticals

Approval Date, If Known June 19, 2008

### 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:

NA

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:

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

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

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

Investigation #1  
IND #                      YES                       ! NO   
! Explain:

Investigation #2  
IND #                      YES                       ! NO   
! Explain:

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

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

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

YES

NO

If yes, explain:

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Name of person completing form: James Moore  
Title: Project Manager  
Date: June 11, 2008

Name of Office/Division Director signing form: Rafel Rieves  
Title: Division Director

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

-----  
**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/

-----  
Rafel Rieves  
6/13/2008 01:52:00 PM

**16. DEBARMENT CERTIFICATION**

**Certification Under Section 306(k)(1) of the FD & C Act**

Bayer HealthCare Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 22-090 that seeks FDA approval of PRIMOVIST® (Gadoxetate Disodium) Injection for use in magnetic resonance imaging (MRI) of the liver.

**BAYER HEALTHCARE PHARMACEUTICALS INC.**

  
\_\_\_\_\_  
Joseph Scheeren, Pharm.D.  
Senior Vice President  
Head of Global Regulatory Affairs

06/12/07  
Date

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-090

Supplement Number: \_\_\_\_\_

NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DMIHP

PDUFA Goal Date:

Stamp Date: July 2, 2007

May 2, 2008

Proprietary Name: Eovist

Established/Generic Name: gadoxetate disodium

Dosage Form: Injection

Applicant/Sponsor: Bayer Healthcare Pharmaceuticals

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

**Q1: Is this application in response to a PREA PMC?**

Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_

Supplement #: \_\_\_\_\_

PMC #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMC?

Yes. **Skip to signature block.**

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):**

(a) NEW  active ingredient(s);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** For use in T1 weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected focal liver lesions.

**Q3: Does this indication have orphan designation?**

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for the remaining pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
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Reason(s) for full waiver: (check, and attach a brief justification)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): \_\_\_\_\_

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.**

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
<input checked="" type="checkbox"/>	Neonate	0 wk. __ mo.	__ wk. 1 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): <u>May 31, 2013</u>								

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

**Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 4/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
  - No: Please check all that apply:
    - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
    - Deferred for the remaining pediatric subpopulations (Complete Sections C)
    - Completed for some or all pediatric subpopulations (Complete Sections D)
    - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
    - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.**

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †	
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
Population	minimum	maximum						
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____								

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

**Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.**

**This page was completed by:**

{See appended electronic signature page}

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 4/2008)

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

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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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Kyong Kang

6/14/2008 08:07:40 AM

## ACTION PACKAGE CHECKLIST

ACTION PACKAGE CHECKLIST		
NDA # NDA # 22-090	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Eovist Established Name: Gadoxetate Disodium Dosage Form: Injection		Applicant: Bayer Healthcare Pharmaceuticals
RPM: James Moore		Division: 160      Phone # (301) 796-2050
NDAs: 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)  (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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):  Provide a brief explanation of how this product is different from the listed drug.  <input type="checkbox"/> If no listed drug, check here and explain:  <b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b>  <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date ❖ Action Goal Date (if different)		PDUFA May 2, 2008 Goal Date June 19, 2008
❖ Actions		
• Proposed action		x AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		x None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		x Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation	
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	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
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:	
Other comments:	
❖ Application Integrity Policy (AIP)	
<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>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ <b>Exclusivity</b></p>	
<ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity?             <ul style="list-style-type: none"> <li>• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> <li>• NDAs: 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> <li>• NDAs: 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> <li>• NDAs: 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> </li> </ul>	<p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes If, yes, NDA # _____ and date exclusivity expires: _____</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes If, yes, NDA # _____ and date exclusivity expires: _____</p>
<p>❖ <b>Patent Information (NDAs and NDA supplements only)</b></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>	<p><input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<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> <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>	<p>21 CFR 314.50(i)(1)(i)(A) N/A</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii)    <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire _____</p>
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] For each <b>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> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>

notice of certification?

(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 to the next section below (Summary Reviews).

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).

- (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?  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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>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 Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<b>Summary Reviews</b>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (<i>indicate date for each review</i>)</p>	<p>DD June 7, 2008 DOD July 1, 2008</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (<i>indicate date</i>)</p>	
<b>Labeling</b>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	<p>x</p>
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	<p>x</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	<p>x NA</p>
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	<p>NA</p>
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	<p>NA</p>
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	<p>X</p>
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	<p>X</p>
<p>❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)</p>	<p>DMETS  <input type="checkbox"/> DSRCS  <input checked="" type="checkbox"/> DDMAC  <input type="checkbox"/> SEALD  <input type="checkbox"/> Other reviews  <input type="checkbox"/> Memos of Mtgs</p>

❖	
<b>Administrative Reviews</b>	
Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	X PM-Filing Review 9-13-08 PLR 9-14-08
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	X Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>Center Director's Exception for Review memo</li> <li>If AP: OC clearance for approval</li> </ul>	NA
❖ Pediatric Page (all actions)	X 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> )	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	X
<ul style="list-style-type: none"> <li>Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	X-Approval Letter
<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	X
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
❖ Internal memoranda, telecons, email, etc.	X
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>EOP2 meeting (<i>indicate date</i>)</li> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	March 14, 2007 none none
❖ Advisory Committee Meeting	X No AC meeting
<ul style="list-style-type: none"> <li>Date of Meeting</li> <li>48-hour alert or minutes, if available</li> </ul>	
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	
<b>Chemistry Review</b>	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	X 4-22-09
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	X None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <li><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>)</li> <li><input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> <li><input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>	See Chemistry Review See Chemistry Review See Chemistry Review pg 109 of 111
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	X (1-4-08)
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: X Acceptable September 24, 2007

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul>	NA <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed (See Chemistry Review) <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<b>Supporting Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	X May 19, 2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	NA
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	NA
❖ ECAC/CAC report/memo of meeting	NA
❖ Nonclinical inspection review Summary (DSI)	NA
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	X Primary-4-25-2008 Secondary-5-19-2008
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	See Clinical Review
❖ Clinical consult reviews from other review disciplines/divisions/Centers ( <i>indicate date of each review</i> )	X April 9, 2008
❖ Microbiology (efficacy) reviews(s) ( <i>indicate date of each review</i> )	X April 25, 2008
❖ Safety Update review(s) ( <i>indicate location/date if incorporated into another review</i> )	X-See Clinical Review
❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> )	X See Clinical Review
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date of each review</i> )	Not needed
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	X
• Clinical Studies	X
• Bioequivalence Studies	NA
• Clin Pharm Studies	NA
❖ Statistical Review(s) ( <i>indicate date for each review</i> )	X May 16, 2008
❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	X May 7, 2008

## Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

**Moore, James W**


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**From:** Moore, James W  
 Wednesday, June 11, 2008 7:18 AM

**To:** Rieves, Rafel

**Cc:** Moore, James W; Kang, Kyong A; Welsh, Cynthia; Harapanhalli, Ravi S; Leutzinger, Eldon E; Choi, Young M; John, Christy; Laniyonu, Adebayo A; Ouyang, Yanli; Mucci, Anthony G; Zalkikar, Jyoti; Marzella, Libero

**Subject:** FW: Eovist - Responses to FDA comments received on 9 May 2008

**Attachments:** Bayer draft 6-10-08 clean(17).doc; Bayer draft 6-10-08 (17).doc; Eovist 10mL Carton D060908b.pdf; Eovist 10mL Vial D060908b.pdf

ere are the labels and revised dates for the PMR as revised by Bayer. It looks like they have provided the info we asked for. Bayer still wants to speak to you sometime today to discuss the application's status. James

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**From:** Ayse Baker [mailto:ayse.baker@bayer.com]  
**Sent:** Tuesday, June 10, 2008 5:05 PM  
**To:** Moore, James W  
**Subject:** Eovist - Responses to FDA comments received on 9 May 2008

Dear Mr. Moore,

Below, please find Bayer's responses to the FDA comments received via fax on 9 June 2008

Revised PI

Revised vial and carton label

Specific Dates for the below items

**Pediatric Observational Study**

The study entitled "an observational study of the administration of Eovist/Primovist in pediatric patients who are referred a contrast enhanced liver MRI because of suspected of known focal liver lesions."

Protocol Submission: 31 November 2008

Study Start: 31 May 2009

Final Report Submission 31 May 2013

Rationale for Study Start: 31 May 2009

As the initial timeline conveyed in the protocol synopsis dated 14 May 2008, Bayer had proposed to submit protocol 6 months after NDA 22,090 approval and proposed to start the study in May 2009. The proposed timelines are consistent with the dates submitted in the protocol synopsis.

Originally, Bayer expected if the NDA was approved in May 2008 (at the time of the submission of the protocol synopsis), protocol could be submitted by November 2008 (six months). While November 2008 is now five months from this

6/11/2008

submission response (June 2008), Bayer is still agreeing to submit the protocol in November 2008. Our original estimate to start in May 2009 was based in part:

time required for review by the FDA of the submitted protocol and time to reach agreement with the FDA on the protocol details

time for review and approval of documents by IRB(s)

other administrative and contractual activities with investigative sites and principal investigators

recruitment of subjects for study start up ( FPFV - First Patient First Visit)

#### . NSF

Clinical trial to assess the magnitude of risk for the development of NSF with Eovist/Primovist among patients with moderate ( GFR < 60 mL/min/1.73 ) to severe renal insufficiency.

Protocol Submission 31 October 2008

Trial start 31 December 2008

Final Report Submission 31 December 2013

#### . Crossover Study

Clinical trial entitled " A single center crossover study to evaluate the possible influence of Erythromycin as an example of inhibitor of the organic anion transporting peptide on the hepatocyte uptake of Eovist in liver MR imaging in healthy subjects"

Protocol Submission: 31 December 2008

Study Start: 31 May 2009

Final Report Submission 31 May 2010

If you have any questions/comments please let me know.

Kind regards, Ayse

---

Ayşe Baker PhD.MBA  
Associate Director  
Nuclear Medicine and Diagnostic Imaging  
Bayer Healthcare Pharmaceuticals  
40 Changebridge Road  
Montville, NJ 07045

Home: 973-487-2566

Mobile: 973-303-6415

Fax: 973-487-2016

E-mail: [ayse.baker@bayer.com](mailto:ayse.baker@bayer.com)

Kind regards, Ayse

Kind regards, Ayse

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**RECORD OF TELEPHONE CONTACT**

**NDA: 22-090**

**Today's date: May 16, 2008**

**Speakers: Dwaine Rieves for FDA and Dr. Eisha Baker for Bayer**

**I called Bayer and told Dr. Baker that FDA had a few additional changes to request for the EOVIIST label and Dr. Moore would forward these (red line) changes shortly. Dr. Baker said Bayer would address/resubmit the label with the changes. I said she could contact me directly for questions at 301-796-1990.**



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:** May 9, 2008

<b>To:</b> Ayse Baker	<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> 973-487-2566	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Fax of Clinical Request for NDA 22,090	

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

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

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**Document to be mailed:**       YES       NO

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May 9, 2008

Regarding your pending NDA 22-090 for Eovist, the Division is requesting additional information. The Division has decided not to grant a waiver of pediatric studies. Instead the Division will grant a deferral of pediatric studies. Thus the following information is needed:

You need to provide a Pediatric Plan to the Division as soon as possible. The plan should include the following elements (1) a description of the study (2) a brief description of study conduct (3) age of patients to be enrolled in the study (4) date the study will begin (5) date of submission of the full protocol (6) date of conclusion of the study and submission of the final study report.

In addition, we are also requesting that you provide a revised REMS for this application.

Please provide this information by COB Wednesday, May 14, 2008.

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

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

**Bayer HealthCare  
Pharmaceuticals**



**UPS Overnight**

Rafel Dwaine Rieves, M.D., Acting Division Director  
Division of Medical Imaging and Hematology Products, HFD-160  
Office of Drug Evaluation III, CDER  
Food and Drug Administration  
Central Document Room  
5901-B Ammendale Rd  
Beltsville, MD 20705-1266

**NDA 22-090  
EOVIST® @ Injection  
(gadoxetate disodium)  
eCTD Sequence No 0034**

**RE: NDA 22-090  
Post Marketing Commitments**

7 May 2008

Dear Dr. Rieves,

Bayer HealthCare  
Pharmaceuticals Inc.  
Global Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Reference is made to NDA 22-090 submitted 29 June 2007. A reference is also made to the Teleconference held on 29 April 2008 to discuss post marketing commitments to NDA 22-090. Specifically, to discuss the uptake of Eovist® in liver with known drugs that are inhibitors of the anionic transporting peptide (OATP) and evaluation of Nephrogenic Systemic Fibrosis (NSF) in association with the administration of Eovist® in patients with moderate to severe renal impairment. Bayer HealthCare Pharmaceuticals Inc., hereby outlines the post marketing commitments for Eovist® below.

Phone: 973 487-2566  
Fax: 973-487-2016  
Email:  
ayse.baker@bayer.com

**1. Evaluation of Eovist® uptake in liver with drugs that are known inhibitors of the anionic transporting peptide (OATP)**

There are several substrates and inhibitors of the organic anionic transporting peptide (OATP) including Erythromycin and some fruit juices, i.e. grapefruit, apple and orange. Among them, Erythromycin is routinely prescribed for respiratory tract infections, severe enteritis, mycoplasma and legionellosis, syphilis, acne and gonorrhea. Therefore, Erythromycin is likely to be used more commonly than Rifampin and its adverse reaction profile is less severe compared to Rifampin. For this reason, the clinical study protocol outline below proposes to select Erythromycin as a representative of OATP in investigation of their possible influence on the hepatocyte uptake of Eovist®/Primovist® in liver MR imaging.



NDA 22-090  
7 May 2008, Page 2 of 3

- Protocol Submission Outline - Draft protocol outline titled "A single center crossover study to evaluate the possible influence of Erythromycin as an example of an inhibitor of the organic anion transporting peptide on the hepatocyte uptake of Eovist®/Primovist® in liver MR imaging in healthy subjects" is provided as Attachment I. Protocol will be submitted within 6 months of the NDA approval .
- Study Start Date (FPFV) - within 12 months after approval of the NDA
- Final Report Submission - within 24 months after approval of the NDA.

**2. Evaluation of Nephrogenic Systemic Fibrosis (NSF) in association with the administration of Eovist® in patients with moderate to severe renal impairment.**

- Protocol Submission - Draft protocol titled " Prospective non-randomized observational (pharmacoepidemiologic) cohort study (open-label, multicenter) to assess the magnitude of potential risk for the development of biopsy-confirmed NSF or cutaneous skin changes consistent with NSF with the administration of Primovist® in patients with moderate and more severe renal impairment." was submitted on 14 December 2007. Per discussions at the T-con held on 29 April 2008 with the Agency, it is our collective understanding that Agency finds the Draft protocol acceptable. With multiple NSF studies using other MR contrast agents already either recruiting patients or in various planning stages; the more limited indication and potential size of the target population of Eovist® compared to extracellular contrast agents; the changing physician practice behaviors regarding at risk patients, and the current worldwide utilization of Eovist®, we propose altering the timelines associated with this study as follows.
- Study Start Date (FPFV) - within 12 months after approval of the NDA. Based on NDA approval of May 2008
  - Start of Study (FPFV) \_\_\_\_\_
  - End of recruitment (LPFV) \_\_\_\_\_
  - End of Study (LPLV) \_\_\_\_\_
- Final Report Submission - \_\_\_\_\_

**Bayer HealthCare  
Pharmaceuticals**



NDA 22-090  
7 May 2008, Page 3 of 3

This documentation is being submitted in eCTD format in accordance with the Guidance for Industry - Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2006). This submission contains 1 CD that has been scanned for viruses using Trend Micro™ Office Scan™, Program Version 7.3.

This CD is being sent to:  
Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Should you have any questions pertaining to this submission, please contact me at (973) 487-2566.

Yours sincerely,  
Bayer HealthCare Pharmaceuticals Inc.

Ayse U. Baker Ph.D., MBA  
Associate Director  
Global Regulatory Affairs



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:** May 6, 2008

<b>To:</b> Ayse Baker	<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> 973-487-2566	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Fax of Information Request for NDA 22,090 (Eovist)	

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

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

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May 6, 2008

In response to your revised labeling provided to the Division on May 5, 2008 for NDA 22,090 (Eovist) the Division has the following information requests.

- A. How was the calculated adverse reaction number of 4.3% derived?
1. Specifically, you should define the adverse reaction population N.
    - a. Does that number include all patients exposed or only the patients who received the proposed dose?
    - b. Does it include all patients who had an adverse reaction or only those the sponsor deemed related?
  2. Email a copy of the table that was used to calculate the numbers (e.g., table ABC, page xxx, from page yyy of the clinical summary of safety).
  3. Provide examples of your calculations.
  4. How many patients who had liver cirrhosis were used to determine that the efficacy and safety were no different?

Please respond to this request as soon as possible.

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

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



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 16, 2008

<b>To:</b> Michele Debartolol	<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) 294-8153	<b>Phone number:</b> (301) 796-2050
<b>Subject:</b> Fax of Statistical Request for NDA 22-090 (Primovist)	

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

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Regarding your pending NDA 22-290 for Primovist, the reviewing statistician has the following request. If the information is already present in the NDA submission, please provide the location of the information.

**Requested Tables**

**For Detection Studies:**

**Gender**

Tables#1 US ; Table#2 EU:

		Lesion Level Detection Rates Averaged over Blinded Readers ( and with 95% two-sided CI's)			
	#Patients	#Lesions	Pre	CT	Pre+Post
Male					
Female					

**Age**

Tables#3 US ; Table#4 EU:

		Lesion Level Detection Rates Averaged over Blinded Readers ( and with 95% two-sided CI's)			
	#Patients	#Lesions	Pre	CT	Pre+Post
<65 yrs					
≥ 65 yrs					

**For Characterization Studies**

**Gender**

Tables#5 US ; Table#6 EU:

		Lesion Level Characterization Rates Averaged over Blinded Readers ( and with 95% two-sided CI's)			
	#Patients	#Lesions	Pre	CT	Pre+Post
Male					
Female					

**Age**

Tables#7 US ; Table#8 EU:

		Lesion Level Characterization Rates Averaged over Blinded Readers ( and with 95% two-sided CI's)			
	#Patients	#Lesions	Pre	CT	Pre+Post
<65 yrs					
≥ 65 yrs					

Please response to this request as soon as possible. You may either provide your response to me electronically at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) or fax it to me at (301) 796-9849. After you have provided this information to me, please follow-up with a submission of this information to the Central Document Room.

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

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

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** March 31, 2008

**TO:** Tiffany Brown, Regulatory Project Manager  
Cynthia Welsh, M.D., Medical Officer  
Division of Medical Imaging and Hematology Products, HFD-160

**THROUGH:** Joseph P. Salewski  
Acting Branch Chief  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

**FROM:** Karen M. Storms, Consumer Safety Officer  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 22-090

**NME:** Yes

**APPLICANT:** Bayer Healthcare Pharmaceuticals

**DRUG:** Primovist Injection

**THERAPEUTIC CLASSIFICATION:** Standard Review, Substantially Equivalent

**INDICATION:** For use in MRI of the liver: \_\_\_\_\_

**CONSULTATION REQUEST DATE:** September 18, 2007

**DIVISION ACTION GOAL DATE:** April 2, 2008

**PDUFA DATE:** May 2, 2008

**I. BACKGROUND:**

Radiologic evaluation for detection of malignant hepatic tumors has become a routine clinical tool. Imaging of liver lesions by CY (computer tomography) and MRI (magnetic resonance imaging) is hampered by the tendency for some lesions to be nearly isodense/isointense (having a radiodensity similar to that of adjacent tissue) normal liver tissue in unenhanced scans, and for certain lesions and normal tissue to have similar enhancement by extracellular contrast agents so that differentiation of tumor from

underlying liver lesions may only be possible using rapid imaging techniques during bolus injection of contrast agents. The characterization of detected liver lesions using extracellular contrast agents has been improved by using gadolinium diethylenetriaminepentaacetic acid dimeglumine (Gd-DTPA) in combination with faster imaging pulse sequences. Gd-EOB-DTPA (SH L 569 B) is also being developed as a liver-specific MRI contrast medium. This agent exhibits not only distribution in extravascular spaces and renal elimination but also selective uptake into the hepatocytes followed by sequestration in the bile. After intravenous injection, Gd-EOB-DTPA is taken up by hepatocytes and thus the contrast between the lesion and surrounding parenchyma (functional tissue of an organ) is increased due to the positive enhancement of the normal liver tissue on T1-weighted MR images. Gd-EOB-DTPA is generally safe and well tolerated.

The protocols covered during these inspections were:

- **Protocol #ME96129**, “A multicenter open-label study with corresponding blinded reading to evaluate SH L 569 B after a single i.v. injection in adult patients with known/suspected focal liver lesions who are scheduled for liver surgery.”
- **Protocol #012387**, “A multicenter (EU) open-label study of Gd-EOB-DTPA with a single intravenous injection (25 µmol/kg body weight) in patients with known or suspected focal liver lesions and the corresponding blinded reading to evaluate the diagnostic efficacy of Gd-EOB-DTPA in the characterization of focal liver lesions.”
- **Protocol #014763**, “A multicenter (US) open-label study of Gd-EOB-DTPA with a single intravenous injection (25 µmol/kg body weight) in patients with known or suspected focal liver lesions and the corresponding blinded reading to evaluate the diagnostic efficacy of Gd-EOB-DTPA in the characterization of focal liver lesions.”
- **#ME97160**, “A multi-center open-label study with corresponding blinded reading to evaluate SH L569 B after a single i.v. injection in adult patients with known/suspected focal liver lesions who are scheduled for liver surgery”

## II. RESULTS (by protocol/site):

Name of CI	City, State*	Protocol #	Insp. Date	Final Classification
Prof. Dr. M. Reiser	München, FRG	ME96129/23	2/25-27/08	Pending
Prof. Roberto Passariello	Rome, Italy	012387/15	3/3-5/08	Pending
David Lu, M.D.	Los Angeles, CA	14763/25	1/29-31/08	NAI
Isaac Francis	Ann Arbor, MI	97160/20	2/15/08-3/6/08	Pending
Donald Mitchell	Philadelphia, PA	14763/14	ongoing	Pending
Bayer Healthcare	Montville, NJ	ME96129 012387 14763 97160 14763	ongoing	Pending

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

### 1. Prof. Dr. M. Reiser, Universitätsklinikum Großhadern, München, FRG - Protocol #ME96129

- What was inspected:** The total number of subjects screened and enrolled at this site was 23. There were 19 subjects completing the study for evaluation for primary efficacy endpoint. 23 subjects'

records were reviewed. There was no evidence of under-reporting of adverse events. The primary efficacy endpoint was verified against original source documents. All subjects received consent prior to procedures being conducted and all subjects met eligibility criteria. Subjects' study records were examined and compared with the corresponding case report forms (CRFs). MRI films were examined and found to be consistent with the CRFs. Blinded reading of the films was performed at a central location and not at the clinical site. The International Trail Manager, Dr. \_\_\_\_\_ was present during the inspection and showed the field investigator the effect of the study drug on visualization of the liver tumor lesions. The local and central ethics committee reviewed and approved the trial and protocol prior to site initiation.

**b. General observations/commentary:** There was no Form FDA 483 issued at the conclusion of the inspection. This site was well monitored. The study records were well organized. In general, the inspection found that the clinical investigator fulfilled his regulatory responsibilities.

**c. Assessment of data integrity:** The inspection did not reveal information that would impact data integrity.

**2. Dr. Roberto Passariello, Universita La Sapienza, Rome Italy - Protocol #012387**

**a. What was inspected:** The total number of subjects screened and enrolled at this site was 15. There were 10 subjects completing the study for evaluation for primary efficacy endpoint. One subject withdrew consent and did not receive study drug; one subject refused to have the Standard of Reference biopsy; one subject had no liver lesion; one subject moved during post-contrast MR; and one subject's MR image had artifacts in the dynamic study images and was deemed unevaluable. 15 subjects' records were reviewed. There was no evidence of under-reporting of adverse events. The primary efficacy endpoint was verified against original source documents. All subjects received consent prior to procedures being conducted and all subjects met eligibility criteria. Subjects' study records were examined and compared with the corresponding case report forms (CRFs). MRI films were examined and found to be consistent with the CRFs. Blinded reading of the films was performed at a central location and not at the clinical site. An Italian official, Maria Antonietta Antonelli, Biold.D., GCP Senior Inspector, GCP/PhV Inspectorate and GCP Promotion Unit, was present during the inspection. The local and central ethics committee reviewed and approved the trial and protocol prior to site initiation.

**b. General observations/commentary:** There was no Form FDA 483 issued at the conclusion of the inspection. This site was well monitored. The study records were well organized. In general, the inspection found that the clinical investigator fulfilled his regulatory responsibilities.

**c. Assessment of data integrity:** The inspection did not reveal information that would impact data integrity.

**3. David S. Lu, M.D., University of California, Los Angeles, CA -Protocol #014763**

**a. What was inspected:** The total number of subjects screened and enrolled at this site was 25 subjects and 25 subjects completed the study. There was 1 death reported (subject 18015 had a malignant hepatocellular carcinoma and subsequently died from cardiac arrest associated with renal failure and sepsis). Subject 18001 and subject 18012 data was not used for analysis due to a major protocol violation and subject 18001 did not receive the Standard of Reference within the 3 month window for a lesion from metastasis. Subject 18012 only received 6.7 ml of test article instead of 7.6 ml. An audit of 25 subjects' records was conducted including source records and case report forms. The CT and MRI films were available upon request.

**b. General observations/commentary:** There was no Form FDA 483 issued at the conclusion of the inspection. This site was well monitored. The study records were well organized. In general, the inspection found that the clinical investigator fulfilled his regulatory responsibilities.

c. **Assessment of data integrity:** The inspection did not reveal information that would impact data integrity.

4. **Isaac Francis, M.D., University of Michigan, Ann Arbor, MI - Protocol ME97160**

a. **What was inspected:** There were 20 subjects enrolled and all 20 subjects receive informed consent. Records reviewed included medical charts, laboratory results, source documents, etc, hard and magnetic tapes of MRI and CT files, completed case report forms, study logs and communication with the sponsor and IRB. The study site was missing hard files and could not download magnetic tapes for subjects 001(MRI), 009 (MRI), 003 (CT), and 006 (CT). Subjects 002, 004, 008 and 018 did not have IOUS/Surgery.

b. **General observations/commentary:** There was a Form FDA 483 issued as the conclusion of the inspection. The violations included not conducting the study according to the investigational plan in that subjects 001, 007, 010, 011, 012, 014, 015, 016, 017, 018, 019, and 020 spiral CT Scan was outside the protocol required Spiral CT scan mAs of 180-300; protocol violations were not reported to the IRB until several years after the study was completed; required patient assessments were missing for subject 02, 05, 06, 012 as required by the protocol

c. **Assessment of data integrity:** The inspection did not reveal information that would impact data integrity. However, because 12/20 subjects' spiral CT Scan were outside the protocol required Spiral CT scan mAs of 180-300 the review division may consider not accepting the data for those 12 subjects.

5. **Donald Mitchell, Thomas Jefferson University Hospital, Philadelphia, PA - Protocol 14763**

a. **What was inspected:** Fourteen subjects were enrolled at this site and all 14 received study drug. Fourteen subjects' records were reviewed. There was no evidence of underreporting of adverse events. Documentation supported that all subjects existed. No test article accountability issues. Informed consent was obtained before all subjects received study drug. Site not involved in blinded reading portion- this was done by a third party.

b. **General observations/commentary:** There was a Form FDA 483 issued at the conclusion of the inspection. According to the protocol exclusion criteria a patient will be excluded from the study if they were participating in a hepatitis Rx clinical trial. Subject 011 was participating in a clinical trial of an investigational drug for hepatitis. In addition it was noted that Dr. Mitchell enrolled a subject that was exposed to test article on 6/19 and was scheduled to undergo chemo embolization to liver on 6/22, so subject 013 missed 72 hour follow up (this was not included on the 483, subject not used in data listings).

c. **Assessment of data integrity:** The inspection did not reveal information that would impact data integrity.

6. **Bayer Healthcare Pharmaceuticals, Montville, NJ**

a. **What was inspected:** The inspection is still ongoing; however, to date, the following has been reviewed for all US sites: all PI CVs/Training; all monitor CV/Training; all IRB approvals; all monitoring reports; all study subject CRF (primary efficacy, AEs) for site 10. (Protocol 14763); software validation for SAE database and clinical database; and reviewed SAEs and AEs during this time. To date, the following has been reviewed for the EU sites: review of all PI CV's; all PI Contracts; Investigator Training Meeting documents to include agendas; all the Ethics documents; the monitoring job qualifications and monitoring CVs (one monitor CV unavailable); Sponsor/PI correspondences; all AEs; and SAEs. In addition for the EU sites: SN 012387 - reviewed the monitoring reports; reviewed the CRFs and monitoring reports; with the aide of the firm's Radiologist reviewed applicable CRF, MRI/CT films for subjects 6012, 6022 (remaining subjects pending review); and reviewed major and minor protocol deviations. For 96129: review of CRFs/Monitoring Reports

(delay with site initiation and next interim monitoring reports, in addition, for 5 out of 8 monitoring reports management review signature is delayed, (by approximately several months); Drug Accountability - reviewed for availability of documentation (pending further review with recently received site shipping documents).

**b. General observations/commentary:** At this time the field investigators are preparing a Form FDA 483 to include the following: For protocol #ME97160, there is no documentation to ensure that IRB approval was maintained throughout the course of the study for 1 out of 13 study centers. For protocol #014763, there is no documentation to ensure that IRB approval was maintained throughout the course of the study for 1 out of 18 study centers.

For protocol #ME97160, Study center #3, consecutive monitoring reports are dated 9/1999 and 5/2000. However, 3 study subjects received study drug on 10/11/99(3009), 11/29/99(3010), and 12/06/99(3011). I'm not sure how I'm going to put this into the citation yet since they do not state specifically what the monitoring frequency will be. But I'm thinking that they should have been out to the site earlier the 5 months after the 12/06/99 enrollment.

For protocol #014763, study center 13, initial IRB approval 2/23/00. Next IRB study review approval dated 5/8/01 to 5/8/02. During this lapse in IRB approval from 2/24/01 to 5/7/01, study subject 13012 received study drug on 3/26/01.

For protocol #ME97160, financial disclosures for clinical investigators were not available for 3 out of 13 study centers. In addition, for protocol #014763, study center #13, a financial disclosure was not obtained from the clinical investigator prior to study subject enrollment.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

With the limited information provided for six above mentioned sites, no major deficiencies were noted that could compromise the integrity of the data. Thus, the data reviewed is acceptable. Should the inspection report contain information that would affect the application, it will be forwarded to the Review Division.

*{See appended electronic signature page}*

Karen M. Storms  
Consumer Safety Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

#### CONCURRENCE:

Supervisory comments

*{See appended electronic signature page}*

Joseph P. Salewski  
Acting Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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/s/

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Karen Storms  
4/3/2008 09:01:28 AM  
CSO

Joseph Salewski  
4/3/2008 01:58:23 PM  
CSO



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: February 28, 2008**

<b>To:</b> Ayse Baker, Ph.D., M.B.A. Global Regulatory Affairs Specialist	<b>From:</b> Tiffany Brown, M.P.H. Regulatory Health Project Manager
<b>Company:</b> Bayer Healthcare Pharmaceuticals	Division of Medical Imaging and Hematology Products
<b>Fax number:</b> 973-487-2016	<b>Fax number:</b> 301-796-1972
<b>Phone number:</b> 973-487-2566	<b>Phone number:</b> 301-796-2050

**Subject:** NDA 22-090 (Primovist®) /FDA Response re Primovist for use as a tradename

**Total no. of pages including cover:** 4

**Comments:** Please provide a response by March 7, 2008. Thank you,

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**Document to be mailed:**       YES                       NO

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To: Ayse Baker, Ph.D., MBA  
Global Regulatory Affairs Specialist  
Oncology and Diagnostic Imaging  
Bayer Healthcare Pharmaceuticals

From: Tiffany Brown, M.P.H.  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

RE: NDA 22-090/Tradename Primovist® Injection/Rejection  
FDA second response regarding tradename review

**Please see comments below:**

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the proposed proprietary name "Primovist" on July 19, 2007, and did not recommend the use of the name from a promotional perspective.

DDMAC objected to the proposed trade name "Primovist" because it overstates the efficacy of the drug product by misleadingly implying it is superior to other treatment options. "Primovist" can be broken down into two parts, "primo" and "vist." "Primo" has various definitions consistent with "the first or leading part." Similarly, "primo" is recognized as a slang term meaning "of the finest quality, excellent" or "exceptionally good of its kind, first class; highly or most valuable." (<http://www.m-w.com/cgi-bin/dictionary>, <http://www.bartleby.com/61/98/P0559800.html>; accessed 7/18/07). "Vist" easily evokes the word "vista," which may be defined as "a view, especially a splendid view from a high position" or a "view through or along an avenue or opening." (<http://dictionary.cambridge.org/define.asp?key=88472&dict=CALD>, <http://www.m-w.com/cgi-bin/dictionary>; accessed 7/18/07). Therefore, the proposed trade name misleadingly implies that this drug product offers the "best or finest view" when performing MRI of the liver, and is thus superior to competitor drug products, when this has not been demonstrated by substantial evidence or substantial clinical experience. In the absence of substantial evidence to support such a superiority claim, the proposed trade name is misleading.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or

substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

The Division of Medical Imaging and Hematology Products (DMIHP) concurred with DDMAC's assessment and communicated the above comments to Bayer HealthCare Pharmaceuticals Inc. (Bayer) on August 1, 2007. Bayer submitted a rebuttal on December 17, 2007. DDMAC has reviewed this rebuttal and offers the following comments.

## PRIMOVIST REVIEW

### Study and Analysis

The website does not elaborate on the evaluation of a trade name for promotional implications. Similarly, the website does not highlight the qualifications of employees in the realm of promotion or advertising. It does, however, reiterate the focus of safety in trade name review activities. The focus on safety, although crucial in the trade name evaluation, does not address all the aspects examined by the FDA in its review of a proposed trade name for suitability.

On behalf of Bayer, conducted a study of 240 U. S. health care practitioners in November 2007 to evaluate "Primovist" to determine if the test name makes claims that are false, misleading, or overly fanciful.

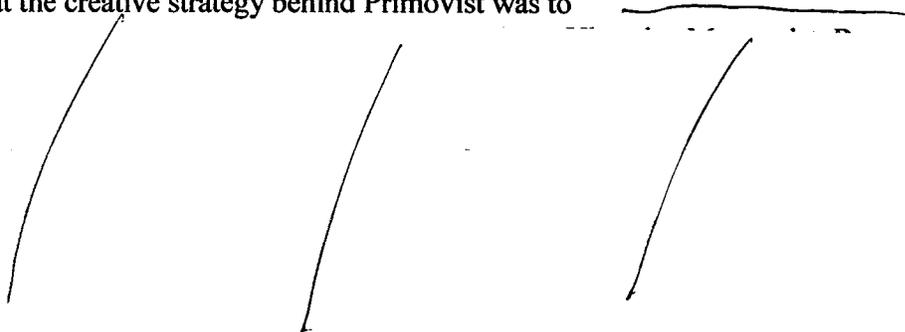
In the materials provided, stated:

Specifically, the majority of the respondents (57.1%) indicated that if "primo" were part of a drug name for an imaging agent, it would not impact their decision to use/prescribe this product. . . To further this point, although 42.9% of respondents indicated that if "primo" were part of a drug name it would impact their decision to use it, a majority of them (56 out of 103) stated either no reason for this decision or came up with very general considerations such as meaningful name, looks promising, good name, sounds safe, sounds basic, like primo, easy to remember, etc. Only two smaller groups of respondents (34 out of 103 and 10 out of 103) indicated that PRIMOVIST suggests a superior product or sounds like a first-line agent.

These cited percentages include a fair percentage of health care practitioners (42.9%) who indicated that if “primo” were part of the drug name it would impact their decision to use/prescribe this product. We note that 54% (56 out of 103) of these respondents stated either no reason for this decision or came up with general considerations (looks promising, like primo, etc); however, this does not mitigate the fact that the name “primo” would impact their decision to use/prescribe this product. In addition a fair percentage of these respondents (33% [34 out of 103] and 9.7% [10 out of 103]) indicated that Primovist suggests a superior product or sounds like a first-line agent. Therefore, based on your analysis, the proposed trade name “Primovist” does affect the judgment of a fair percentage of health care practitioners to use or prescribe this product.

Furthermore, the materials provided state, “The product demonstrates the following key **advantages over other existing products . . .**” and “The prefix “PRIMO” captures that this product is the **FIRST/BEST/PREMIUM** (or PRIMO) gadolinium-based agent for the detection and characterization of focal liver lesions.” (emphasis added) However, we are not aware of substantial evidence to support that Primovist is superior to other treatment options.

Bayer states that the creative strategy behind Primovist was to



In conclusion, DDMAC continues to maintain its objection to the proposed trade name “Primovist” because it overstates the efficacy of the drug product by misleadingly implying it is superior to other treatment options.

We request that you submit two alternative names to the Division of Medical Imaging and Hematology Products for review by March 7, 2008.

If you have any questions, please contact Tiffany Brown, Regulatory Health Project Manager at 301-796-2050.

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<sup>1</sup> Please note that DDMAC is not objecting to the “vist” portion of the proposed drug name.

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/s/

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Tiffany Brown  
2/28/2008 11:27:46 AM  
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

## REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: ODS

FROM: Tiffany Brown, Regulatory Health Project Manager,  
Division of Medical Imaging and Hematology Products

DATE  
01/09/08

IND NO.

NDA NO.  
22-090

TYPE OF DOCUMENT  
4S

DATE OF DOCUMENT  
December 12, 2007

NAME OF DRUG  
Primovist (proposed tradename)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
1S

DESIRED COMPLETION DATE  
02/09/08

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 II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> * OTHER (SPECIFY BELOW):      |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- DISSOLUTION  
 BIOAVAILABILITY STUDIES  
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE  
 PROTOCOL-BIOPHARMACEUTICS  
 IN-VIVO WAIVER REQUEST

#### IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL  
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES  
 CASE REPORTS OF SPECIFIC REACTIONS (List below)  
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY  
 SUMMARY OF ADVERSE EXPERIENCE  
 POISON RISK ANALYSIS

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

#### COMMENTS/SPECIAL INSTRUCTIONS:

Bayer Pharmaceuticals, Inc. has submitted a Risk Management Plan to assess the risk for NSF patients with varying degrees of renal insufficiency. This submission may be located in the EDR, Global Submit Review, under amendment 0015, dated December 14, 2007.

Should you have any questions, please contact me at 301-796-1972. Thank you.

SIGNATURE OF REQUESTER  
Tiffany Brown, Regulatory Health Project Manager, DMIHP

METHOD OF DELIVERY (Check one)  
 DFS  MAIL  HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

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Tiffany Brown  
1/9/2008 02:47:13 PM

# REQUEST FOR CONSULTATION

TO (Division/Office):

**CDER OSE CONSULTS**

FROM: Alice Kacuba on behalf of Tiffany Brown

DATE  
12-27-07

IND NO.

NDA NO.  
22-090

TYPE OF DOCUMENT  
C-request retention of  
Primovist as tradename

DATE OF DOCUMENT  
12-17, 2007

NAME OF DRUG  
Primovist Injection

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
pharm stress agent

DESIRED COMPLETION DATE  
March 1, 2008

NAME OF FIRM: Bayer HealthCare

## 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 II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                                     |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                                |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW   |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>Trade name review</b> |
| <input type="checkbox"/> MEETING PLANNED BY            |  |   |

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

### IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Sponsor requests retention of Primovist as tradename. 12-17-07 submission in edr.

PDUFA DATE: April 24, 2008 but action package and letter must circulate by March 27, 2008.

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA 22090

HFD-160/Division File

HFD-160/RPM

HFD-160/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER  
Alice Kacuba on behalf of Tiffany Brown

METHOD OF DELIVERY (Check one)

DFS ONLY

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SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

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Alice Kacuba  
12/27/2007 05:46:48 PM



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 20, 2007

<b>To:</b> James Hoover Global Regulatory Affairs	<b>From:</b> Tiffany Brown, M.P.H. Regulatory Health Project Manager
<b>Company:</b> Bayer HealthCare Pharmaceuticals, Inc.	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> 973-487-2208	<b>Phone number:</b> 301-796-1972
<b>Subject:</b> NDA 22-090 (PRIMOVI <sup>®</sup> )/CMC Information Request Letter/DMF	

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

**Comments:** If you have any questions, please contact me at 301-796-1972.

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**Document to be mailed:**       YES       NO

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(A)

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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/s/

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Tiffany Brown  
11/20/2007 12:57:17 PM



renal insufficiency (i.e., mild, moderate, severe). We request that you submit a protocol concept sheet of a registry study for our review.

**Pharmacology/Toxicology:**

We have noted that some safety pharmacology and toxicology studies were not adequately designed. For example, Study DERA 1004 used 2 dogs/sex/group only. In addition, non-English certificate has been identified. However, considering the fact that similar studies were conducted using both formulation SHL569A and SHL569B and the totality of available safety information for this class drug, these deficiencies will be treated as review issues rather than fileable issues. Please be advised that additional information may be requested during the review process.

**Chemistry, Manufacturing and Controls:**

1. From what you are saying in the submission, you consider the 60 months of stability data from the \_\_\_\_\_), the "old" production site, as primary stability data in support of a proposed expiration date of 60 months for drug product in the following presentations: \_\_\_\_\_ 10 mL in 10 mL glass vials,

\_\_\_\_\_ We have the following questions:

- a. Was the equipment used for production of product at \_\_\_\_\_ the same in type and design, and principle of operation?
- b. Is the container closure made of the same materials and from the same sources between \_\_\_\_\_ and \_\_\_\_\_
- c. Was the \_\_\_\_\_ in drug product from old site also produced at \_\_\_\_\_
- d. It is our understanding that there have been no changes in the formulation of drug product between \_\_\_\_\_; and \_\_\_\_\_ Elaborate if any changes have been made.
- e. Have there been any changes in major suppliers of materials for production of either drug substance (Gd-EOB-DTP) or drug product. For example, is the supplier / manufacturer of \_\_\_\_\_ for product at \_\_\_\_\_ the same as it was for product manufactured at \_\_\_\_\_

2. In 3.2.P.8.2 (Post-approval Stability Protocol and Stability Commitment), you state that "ongoing stability studies for production plant batches \_\_\_\_\_) will be continued according to the testing up to 60 months." It is not clear why \_\_\_\_\_ is included within this stability commitment, because the stability data you have from that site is already for 60 months. Explain. Do you have plans to do additional stability studies at the \_\_\_\_\_ plant and for what purpose?

**Microbiology:**

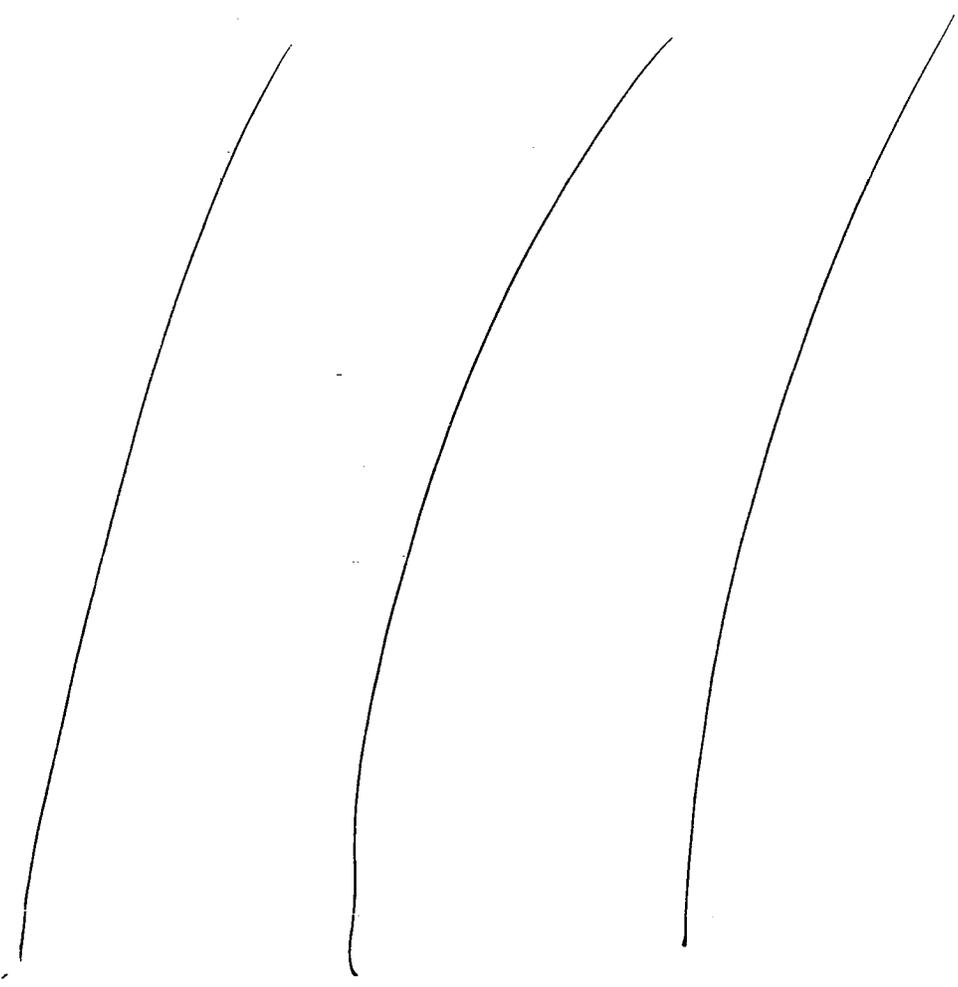
Provide detailed summaries of the following:

1. Validation of the \_\_\_\_\_
2. Validation of the \_\_\_\_\_ sterilization of the drug product in vials

Please refer to the FDA "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" for recommendations on the specific information to provide.

**Labeling (Please provide an updated label by November 19, 2007):**

The following issues/deficiencies have been identified in your proposed labeling.



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.

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.

If you have any questions, call Tiffany Brown, Regulatory Project Manager, at (301) 796-1972.

Sincerely,

*{See appended electronic signature page}*

Kyong, "Kaye" Kang, Pharm.D.  
Chief, Project Management Staff  
Division of Medical Imaging and  
Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/

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Kyong Kang

9/14/2007 02:34:24 PM

# REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

**Division of Medical Imaging and Hematology Products**

**Application Number:** NDA 22-090

**Name of Drug:** PRIMOVIST® INJECTION (Gadoxetate Disodium)

**Applicant:** Bayer HealthCare Pharmaceuticals Inc.

## **Material Reviewed:**

**Submission Date(s):** June 29, 2007

**Receipt Date(s):** July 2, 2007

**Submission Date of Structure Product Labeling (SPL):** June 29, 2007

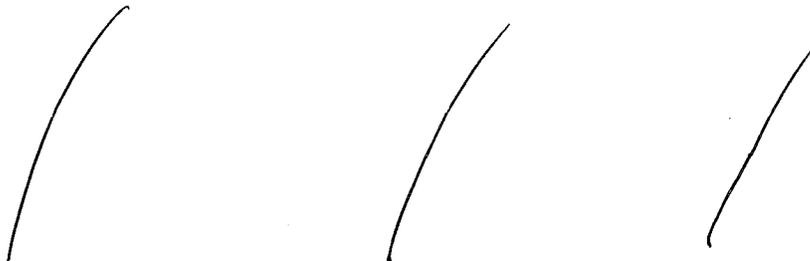
**Type of Labeling Reviewed:** WORD AND SPL

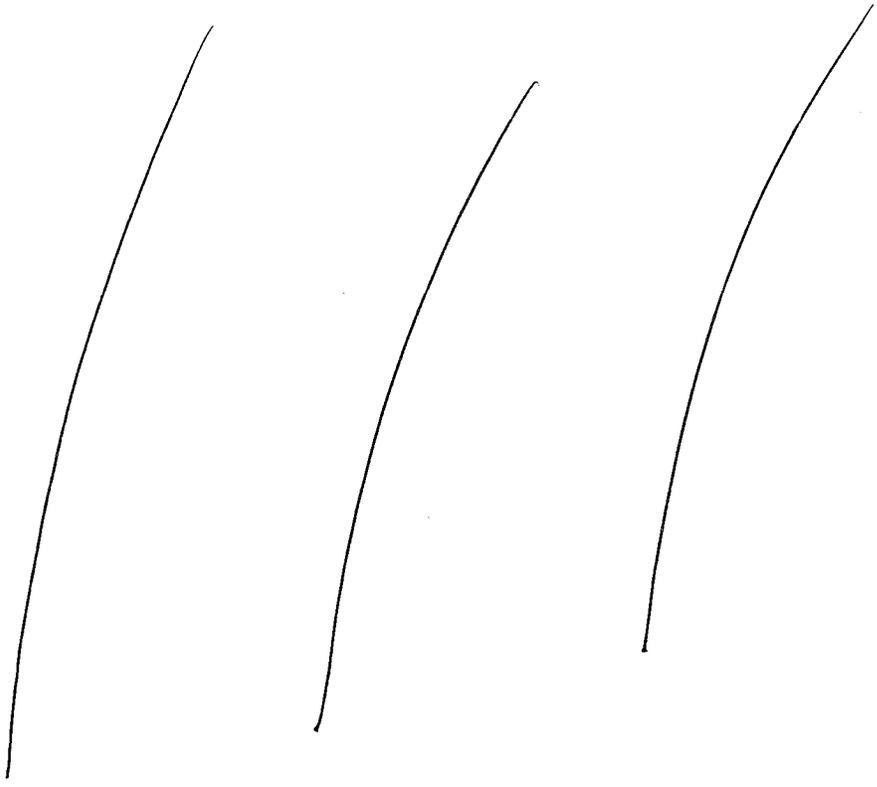
## **Background and Summary**

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

## **Review**

The following issues/deficiencies have been identified in your proposed labeling.





**Recommendations**

Please address the identified deficiencies/issues and re-submit labeling by November 19, 2007. This updated version of labeling will be used for further labeling discussions.

Tiffany Brown, M.P.H.

\_\_\_\_\_  
NAME OF REGULATORY PROJECT  
MANAGER

Supervisory Comment/Concurrence:

Kyong "Kaye" Kang

\_\_\_\_\_  
NAME OF CHIEF PROJECT MANAGER  
Chief, Project Management Staff

Drafted: Tiffany Brown, September 13, 2007

Revised/Initialed: KK/September 14, 2007

Finalized: TB/September 14, 2007

Filename: NDA 22-090 (Primovist)CSO Labeling Review for 74 Day Letter.doc

**CSO LABELING REVIEW OF PLR FORMAT**

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/s/

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Tiffany Brown  
9/14/2007 12:12:03 PM  
CSO

Kyong Kang  
9/14/2007 02:28:07 PM  
CSO



*Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, 5 Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 54, 875
- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) February 14, 2007 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: August 27, 2007

NDA #: 22-090

DRUG NAMES: PRIMOVIST® Injection (Gadoxetate Disodium)

APPLICANT: Bayer HealthCare Pharmaceuticals

BACKGROUND: Primovist® Injection is an aqueous solution containing the new gadolinium chelate gadolinium-EOB-DTPA.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Dwaine Rieves; Cynthia Welsh; Yanli Ouyang; Eldon Leutzinger; Christy John; Jyoti Zalkikar; Anthony Mucci; Kaye Kang and Tiffany Brown

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Cynthia Welsh
Secondary Medical:	
Statistical:	Anthony Mucci
Pharmacology:	Yanli Ouyang
Statistical Pharmacology:	
Chemistry:	Eldon Leutzinger
Environmental Assessment (if needed):	
Biopharmaceutical:	Christy John
Microbiology, sterility:	Bryan Riley
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Tiffany Brown
Other Consults:	

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain:
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE   
 STATISTICS N/A  FILE  REFUSE TO FILE   
 BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed?  
YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO
- Sterile product? YES  NO
- If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**  
Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**  
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.  Convey document filing issues/no filing issues to applicant by Day 74.

Tiffany Brown, DMIHP  
Regulatory Project Manager

**APPEARS THIS WAY  
ON ORIGINAL**

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

**APPEARS THIS WAY  
ON ORIGINAL**

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product? YES  NO

*If "Yes" contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

*If "Yes," to (c), proceed to question 7.*

*NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

*If "No," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is YES  NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? YES  NO   
(This is different from the patent declaration submitted on form FDA 3542 and 3542a.)

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

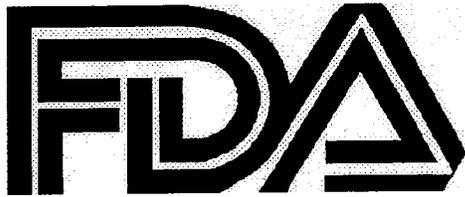
If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

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Tiffany Brown  
9/13/2007 10:07:35 AM  
CSO



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: August 1, 2007

<b>To:</b> Sibylle Jennings, Ph.D. c/o Shelly Fehr	<b>From:</b> Tiffany Brown, M.P.H.
<b>Company:</b> Bayer Healthcare Pharmaceuticals, Inc.	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> NDA 22-090 (Primovist® Injection) - Tradename	

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

**Comments:** If you have any questions, please contact me. Thank you.

---

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**Document to be mailed:**       YES       NO

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-090

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Sibylle Jennings, Ph.D.  
Global Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Dear Dr. Jennings:

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

This letter is to inform you that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has objected to the use of Primovist as a tradename for the reasons outlined below.

DDMAC objects to the proposed trade name "Primovist" because it overstates the efficacy of the drug product by misleadingly implying it is superior to other treatment options. "Primovist" can be broken down into two parts, "primo" and "vist." "Primo" has various definitions consistent with "the first or leading part." Similarly, "primo" is recognized as a slang term meaning "of the finest quality, excellent" or "exceptionally good of its kind, first class; highly or most valuable." (<http://www.m-w.com/cgi-bin/dictionary>, <http://www.bartleby.com/61/98/P0559800.html>; accessed 7/18/07). "Vist" easily evokes the word "vista," which may be defined as "a view, especially a splendid view from a high position" or a "view through or along an avenue or opening." (<http://dictionary.cambridge.org/define.asp?key=88472&dict=CALD>, <http://www.m-w.com/cgi-bin/dictionary>; accessed 7/18/07). Therefore, the proposed trade name misleadingly implies that this drug product offers the "best or finest view" when performing MRI of the liver, and is thus superior to competitor drug products, when this has not been demonstrated by substantial evidence or substantial clinical experience. In the absence of substantial evidence to support such a superiority claim, the proposed trade name is misleading.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

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

Sincerely,

*{See appended electronic signature page}*

Tiffany Brown, M.P.H.  
Regulatory Health Project Manager  
Division of Medical Imaging and  
Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/

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Tiffany Brown  
8/1/2007 11:28:12 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 22-090

**NDA ACKNOWLEDGMENT**

Bayer HealthCare Pharmaceuticals Inc.  
Attention: Sibylle Jennings, Ph.D.  
Global Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Dear Dr. Jennings:

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

Name of Drug Product: PRIMOVIST® Injection (Gadoxetate Disodium)

Review Priority Classification: Standard (S)

Date of Application: June 29, 2007

Date of Receipt: July 2, 2007

Our Reference Number: NDA 22-090

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 August 31, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 2, 2008.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

NDA 22-090

Page 2

Please cite the NDA number listed above 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 and Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1972.

Sincerely,

*{See appended electronic signature page}*

Tiffany Brown, M.P.H.  
Regulatory Health Project Manager  
Division of Medical Imaging and  
Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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

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Tiffany Brown  
7/12/2007 11:53:13 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 54, 875

Berlex, Inc.  
Attention: Sibylle R. Jennings, Ph.D.  
Associate Director, Global Regulatory Affairs  
P.O. Box 1000  
Montville, NJ 07045-1000

Dear Dr. Jennings:

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

We also refer to the meeting between representatives of your firm and the FDA on February 14, 2007. The purpose of the meeting was to acquaint the reviewers with the content, presentation and format of NDA 22-090 and to discuss specific, primarily format related questions prior to the NDA submission.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

*{See appended electronic signature page}*

Tiffany Brown, M.P.H.  
Regulatory Health Project Manager  
Division of Medical Imaging and  
Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure

**DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS**

**PRE-NDA TELECONFERENCE**

**MEMORANDUM OF MEETING MINUTES**

**APPLICATION:** IND 54,875

**DRUG:** PRIMOVIST®

**DATE:** 02/14/07

**Meeting Participants:**

**Name:** Dwaine Rieves, MD, Acting Division Director  
Louis Marzella, MD, Acting Deputy Division Director  
Cynthia Welsh, MD, Clinical Reviewer  
Jyoti Zalkikar, Ph.D., Statistical Team Leader  
Anthony Mucci, Ph.D., Statistical Reviewer  
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Christy John, Ph.D, Clinical Pharmacologist  
Eldon Leutzinger, Ph.D., ONDQA, Pharmaceutical Assessment Lead  
Gary Gensinger, OBPS/RRSS  
Tiffany Brown, M.P.H., Regulatory Health Project Manager

**Representing:** The Division of Medical Imaging and Hematology Products

**Name:**

Josy Breuer, M.D., Executive Director, Medical Development  
Suming Chang, Ph.D., Director, Statistics  
Shelly Fehr, Senior Associate, Global Regulatory Affairs Imaging  
Sibylle Jennings, Ph.D., Associate Director, Global Regulatory Affairs  
Jens Leopold, Ph.D., Director, Global Regulatory Affairs Diag. Imaging  
Patricia Mayer, Ph.D., Director, Global Regulatory Affairs Diagnostic  
Karen Mastrofilipo, Manger, Regulatory Electronic Submissions  
Louis Mylecraine, Ph.D., Director, Nonclinical Development  
Andreas Schliwa, Ph.D., Director, Global Process Coord. and Quality  
Ann Tomaszkeski, Associate, Regulatory Electronic Submissions

**Representing:** Berlex, Inc. and Bayer Schering Pharma AG

**DISCUSSION:** The focus of the discussion points during the meeting concerned a discussion of the items presented in the Division comments sent via facsimile on February 9, 2007. The Division responses are attached in Appendix I.

The Sponsor began the meeting by providing the Division with an overview of the number of eCTD (electronic common technical documents) that the Sponsor has submitted to the Agency. The Sponsor has submitted over eighty eCTDs to the Agency; however, the Sponsor noted that this will be the first eCTD submission made to the Division of Medical Imaging and Hematology Products (DMIHP).

**I. Handout and Reviewer's Guide:** This will be submitted to the NDA as an appendix. It contains specifics on how the eCTD was compiled. The Handout and Reviewer guide include but are not limited to the following information.

- 1) A very compressed list of clinical study reports which includes both the study report and protocol numbers.
- 2) All pivotal studies included as text-based numbers.

**II. CMC (Chemistry, Manufacturing and Controls)**

**Drug Substance:** The Sponsor stated that Primovist is ———. Furthermore, the Sponsor stated that Drug Master File (I) has already been submitted and that the second Drug Master File (II) will be submitted this month (February 2007).

- The Sponsor intends to provide general information in the eCTD regarding the drug substance.
- The Sponsor will also provide a Certificate of Analysis (COA) that demonstrates the results from the reference standard.
- In the testing summary section, the Sponsor provides methods for the identification of the drug substance content as well as five different methods for testing the impurities for this drug substance.

**Acceptance Criteria:** The Sponsor stated that this section describes the evaluation criteria, and the Sponsor intends to use this quality test evaluation as described in the testing standard for the identification test.

- The Sponsor confirmed that the eCTD will have full discussion of the synthesis and the acceptance criteria.

**Non-clinical:**

The Sponsor stated that this section of the reviewer's guide is quite detailed. The Sponsor then proceeded to describe some of the important linking strategies within this section of the eCTD.

The Sponsor stated that there are two links for every study described in the text:

1. First, a link directly to the study report in Module IV; and
2. Secondly, a link to respective tabulated summaries located in Module II and a link to the source document in Module IV.

The Sponsor stated that the other linking strategies are similar to how the linking strategies are described in the reviewer's guide.

- The Sponsor plans to exchange the tables currently located in the non-clinical section to the more extensive tables discussed with the Pharmacology/Toxicology team during a previous teleconference held December 14, 2006.
- The Sponsor stated that the new summary tables will contain information on impurities and the formulation that was tested.
- Module IV: The Sponsor stated that certain sections have been removed from this module since the sponsor never studied excretion or metabolism exclusively. Thus, there is only one section which is entitled "absorption and distribution".

The Sponsor stated that all of this information is discussed in the reviewers guide.

**Clinical:**

**Sponsor Question E1:** Does the Division agree to the proposed documentation and content of the SAS datasets?

**FDA Response to Question E1:** The Agency stated that the statistical team would have to review what is submitted with the eCTD and then discuss the details as to the lay-out of the data. The Agency provided an example such that if we are thinking of a primary efficacy analysis, the assumption is that there is one line of data that will be dedicated to each patient.

**FDA Question:** Is this the basic format for the efficacy data?

**Sponsor Response:** Yes, this is the format of the efficacy data.

**FDA Comment:**

The Agency stated that the statisticians may request other formatting for the data to make the analyses simpler from a statistical point of view.

**Sponsor Comment:**

The Sponsor stated that to facilitate the Agency's review of the submission, the Sponsor would be willing to provide any additional information.

**FDA Comment:** With regard to your question E1 (concerning the proposed documentation and content of the SAS datasets) we request that for each relevant study report you provide the following:

- a) A written statement certifying that the datasets are consistent with FDA guidance on study data specifications (see eCTD guidance)
- b) A complete description of the procedures for quality controls for the datasets (including verification of data entry from CRF, tracking and reconciliation of inconsistencies)

In addition, to facilitate our review of analyses and summaries of data in the efficacy study reports we request that you consider providing a reference (footnote) describing the supporting data sets and the programs used to generate each of the figures and tables.

**FDA Question:** Are the datasets in the XPT format; and if so could you please describe the software that was used to create these datasets?

**Sponsor Response:** Yes, the datasets are in .XPT format.

**FDA Comment:** Please make sure that the clinical and statistical reviewers will be able to use JMP to open up the data sets for simple navigation. We provide the following link for your reference.

<http://www.fda.gov/cder/regulatory/ers/ectd/htm>

This website provides links to the guidance to Industry for electronic submission of datasets, and links to the website that provides information on STDM standard that the sponsors need to use to create these datasets and guidance on creating the data definition file. Even if the NDA submission is not electronic, the datasets that are electronically submitted should be consistent with the guidance.

**Sponsor Response:** The Sponsor plans to submit the data sets according to the guidance.

**FDA Comment:** The Agency reminded the Sponsor to be sure that data definitions of the SAS data variables are included.

**FDA Question:** The Agency inquired whether there would be a notation made for each table to designate data-source?

**Sponsor Response:** The Sponsor stated that the program is based on each dataset, and the tables will be organized according to each dataset.

**FDA Question:** Have you documented how the tables were created?

**Sponsor Response:** The Sponsor stated that it was their understanding that this information was not a requirement.

**FDA Comment:** The FDA stated that although it is not a requirement, it is always helpful to be able to access the dataset that was used to construct a particular table.

**Sponsor Questions E2 and E3:**

**Question E2a:** Does the Division agree that this is an appropriate approach in the case of Primovist? and **Question E2b:** Does the Division prefer to have this document in Module 2 and in Module 5 of the Primovist eCTD?

*Division reply: We agree with your proposal to place the ISS report (including important text tables) in Module 2 with cross reference to additional tables in Module 5. We request that you provide the complete report (text, important text tables and appendix) as a full-standing document (one electronic file) in Module 5.*

**Question E3:** Does the Division agree that separate ISE in Module 5 is not warranted in this case?

*Division Reply: No. A separate ISE should be included in Module 5. Please confirm that you will provide detailed side-by-side tabular presentation of the efficacy studies highlighting important similarities and differences in study protocol, study conduct, patients' disposition, and important efficacy outcomes. Please clarify whether you will conduct exploratory analyses of pooled data in specific subgroups (e.g. geographic region, race gender, age, clinical diagnosis).*

**The Sponsor began the discussion of these two questions with the following statements.**

- The Sponsor would like to assure the FDA that the level of detail contained in this summary document equals the amount of detail that we put into an ISS report.
- The Sponsor stated that the efficacy summary is not very long—approximately 210 pages. Additionally, the Sponsor stated that they still have to include some information on the Pharmacology/Toxicology studies.
- The Sponsor stated that the safety summary is complete and is approximately 170 pages.
- For the ISS, The Sponsor stated that they have the ISS (Integrated Safety Summary) tables and a reference to the tables with hyperlinks from the summary documents. These documents have a hyperlink to the tables in Module V.
- For the ISE (Integrated Safety of Efficacy), the Sponsor stated that there are datasets underneath each study and the Sponsor refers mainly to chapter 14 of the individual studies which are hyperlinked. The only efficacy tables are post-tox frequency studies.

**FDA Comments:**

- In Module V, you need a file that links ancillary files with the ISS documents.
- To make a document functional, we would like to see it contain all of the main tables as opposed to a “click” and then taken into another hyperlink.

**Sponsor Response:**

We have included all relevant tables as “text tables”.

**FDA Question:**

Are the tables referenced in the text?

**Sponsor Response:**

YES, all tables are referenced and included in the text.

Question E4: Is this approach acceptable to the Division?

*Division reply: Please provide an additional analysis of adverse events that includes all patients exposed to the contrast agent.*

Sponsor Response: We have two separate ISS analyses; one for healthy volunteers and one for patients. The Sponsor stated that this information could be found in the section entitled “ISS conducted on patients”.

Question E5: Is this acceptable to the Division?

*Division reply: Please provide the adverse event terms used in all study reports and tables according to MedDRA format. Please provide a coding dictionary that includes verbatim → preferred term and preferred term → verbatim.*

Question E5 Discussion: The Sponsor stated that for the information contained in the individual study reports is not coded using MedDRA but the “heart” terminology. The Sponsor acknowledged that this may be a problem for the reviewers, and the Sponsor agrees with the Agency’s comment on this question. The Sponsor asked if the Agency would please review the correlation table and explain how the Agency would prefer to view the arrangement of the table.

The Agency stated that the Sponsor should provide the tables based upon the MedDRA terminology. At first glance, there do not appear to be any material differences. In principle, we would like to see the official terminology in the study reports.

FDA Comment: In the summary of safety, you have provided tabular presentations based on the MEDDRA terminology but in the individual study reports, the terminology is based on the “HARTS” terminology. Would it be possible to provide in each study report, tables based on the MedDRA terminology? Finally, the FDA staff recommended that we move on to other issues

and leave this issue unresolved given that the Agency does not see a lot of difference between the two types of terminology, the Agency may be satisfied with what the Sponsor has provided.

**Question E6:** Does the Division agree that the ECG database as obtained during the development of Primovist is sufficient for filing the NDA?

**FDA Response:**

This Agency stated that this will be a review issue.

**ADDITIONAL COMMENTS**

*1. Please confirm that you will provide a summary of global safety data including listings and summaries of adverse events, clinical summaries of serious adverse events and exposure data. In light of the associations between gadolinium agents and the development of nephrogenic systemic fibrosis (NSF), please include a summary of searches of your database and of the literature for cases of NSF and include a description of your search strategy including search terms.*

**Sponsor response:** There Sponsor stated that there have been no cases of NSF for Primovist. The Sponsor stated that the firm would include a summary that identifies a search of NSF cases and this information would be included the under the section entitled “post-marketing.”

- The Sponsor stated that there will be a hyperlink to the NSF issue.

*2. Please include a detailed global table of contents of the submission. Please include page and volume number next to each listing.*

**Sponsor response:** The Sponsor intends to provide the Agency with a global table of contents and will place this information in the reviewer’s guide as an additional appendix.

*3. When writing the Integrated Summary of Safety, please include hyperlinks to the narratives and the case report forms (CRFs).*

*4. Please include CRFs and narrative summaries for the serious adverse events, and discontinuations and drop-outs as well.*

**Sponsor Response to FDA Questions #3 and #4:**

The Sponsor stated that the firm will follow the Agency’s advice.

5. *You state that you propose to address in the NDA our information requests of April 20, 2006 and of September 20, 2006. Please provide a listing of our requests and a summary of your planned responses. Please indicate in which section of the NDA submission you will provide this information.*

**Sponsor Response to FDA Question #5:**

The Sponsor stated that the post-hoc analysis is still ongoing, and the Sponsor intends to include in the NDA submission responses to the Agency's information requests of April 18, 2006 and September 20, 2006. The Sponsor also intends to indicate in the NDA submission where the responses can be located.

**[B1]-Pediatric Studies Discussion:**

**Sponsor Comment:**

The Sponsor stated that the firm would like to inform the Agency that the firm does not have experience with the use of Primovist in pediatric patients. The Sponsor stated that it will more than likely be impossible to recruit pediatric patients in order to conduct a meaningful study. Therefore, the Sponsor plans to submit a request for a waiver from the requirement to assess the safety and effectiveness of new drugs in pediatric patients.

**FDA Response:**

The Agency acknowledged an appreciation for the difficulty associated with conducting a prospective study. The Agency inquired as to whether the Sponsor could collect some data retrospectively. The FDA closed by stating that this will have to be discussed in more detail at a later time.