

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-711**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-711

SUPPL #

HFD # 160

Trade Name Vasovist

Generic Name Gadofosveset Trisodium

Applicant Name Epix Pharmaceuticals, Inc.

Approval Date, If Known December 22, 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:

d) Did the applicant request exclusivity?

YES  NO

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

5 years

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

YES  NO

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

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

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

YES  NO

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

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

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1

YES   
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: October 16, 2008

Name of Office/Division Director signing form: Richard Pazdur  
Title: Office Director, Office of Oncology

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

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

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Richard Pazdur  
12/22/2008 09:10:48 AM

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21711

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

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

Division Name: DMIHP

PDUFA Goal Date: 12/31/08

Stamp Date: 7/1/2008

Proprietary Name: Vasovist

Established/Generic Name: Gadofosveset Trisodium

Dosage Form: Injection

Applicant/Sponsor: Epix Pharmaceuticals, Inc.

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

(1) NA

(2) NA

(3) NA

(4) NA

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): \_\_\_\_\_

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

**Indication:** 1 Vasovist Injection is a gadolinium-based blood pool contrast agent indicated for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease.

**Q1:** Is this application in response to a PREA PMR? Yes  Continue

No  Please proceed to Question 2.

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

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

PMR #: \_\_\_\_\_

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

Yes. Please proceed to Section D.

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) (includes new combination);  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.**

**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 some or all 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 for the reason(s) selected)

- 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 unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and 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.*

**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	1 yr. __ mo.	2 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 for each reason):  
 IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

**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 unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*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 complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (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 Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section 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 selected pediatric subpopulations).**

Check pediatric subpopulation(s) 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)*	Received
<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"/>
<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"/>
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 partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

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 checked="" type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input checked="" 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: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

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

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 all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or 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 pediatric subpopulation for which information will be extrapolated. 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*

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmps@fda.hhs.gov](mailto:cderpmps@fda.hhs.gov)) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

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 or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**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 some or all 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 for the reason(s) selected)

- 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 unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and 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.*

**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 unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (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 Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (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 Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

proceed to Section 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 some or all pediatric subpopulations).**

Check pediatric subpopulation(s) 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)*	Received
<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"/>
<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"/>
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 partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

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: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

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

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 all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or 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 pediatric subpopulation for which information will be extrapolated. 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. Under the statute, safety cannot be extrapolated.*

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 or DARRTS as appropriate after clearance by PeRC.***

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: 6/2008)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

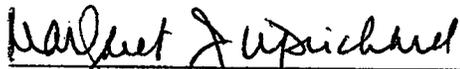
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/s/

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Kyong Kang  
12/19/2008 10:11:52 AM

To Whom It May Concern:

EPIX 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 this application.



Margaret J. Uprichard, PharmD  
Senior Vice President  
Regulatory Affairs and Quality

27 Jun 2008  
Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-711

Epix Pharmaceuticals  
Attention: Margaret Uprichard, PharmD.  
Senior Vice President  
Regulatory Affairs and Quality  
4 Maguire Road  
Lexington, MA 02421

Dear Dr. Uprichard:

We acknowledge receipt on July 1, 2008 of your June 30, 2008 resubmission to your new drug application for Vasovist®, (Gadofosveset Trisodium) Injection.

We consider this a complete, class 2 response to our November 21, 2005 action letter. Therefore, the user fee goal date is December 31, 2008.

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.

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

Sincerely,

*{See appended electronic signature page}*

James Moore, PharmD., M.A.  
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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James Moore  
7/24/2008 09:54:08 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-711

Epix Medical, Inc.  
Attention: Robert A. Morgan  
Executive Director, Regulatory Affairs and Quality  
71 Rogers Street  
Cambridge, MA 02142

Dear Mr. Morgan:

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:	VASOVIST™, (Gadofosveset Trisodium) Injection 0.25mmol/mL
Review Priority Classification:	Standard (S)
Date of Application:	December 12, 2003
Date of Receipt:	December 15, 2003
Our Reference Number:	NDA 21-711

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 February 13, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 15, 2004.

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.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160  
Attention: Division Document Room, 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160  
Attention: Document Room 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call CAPT James Moore, Regulatory Project Manager, at (301) 827-6254.

Sincerely,

*{See appended electronic signature page}*

Patricia Stewart  
Acting Chief, Project Management Staff  
Division of Medical Imaging and  
Radiopharmaceutical Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Patricia Stewart  
1/23/04 03:41:54 PM

Mid-Cycle Meeting for Vasovist, NDA 21-711, Thursday, November 13, 2008,  
Conference Room 1421, Building 21, White Oak Campus, Silver Spring, Maryland

The following FDA Staff attended the Mid-cycle presentation for this pending application.

Richard Pazdur, M.D, Office Director, Oncology  
Charles Ganley, M.D, Office Director, Non-Prescription Drugs  
Rafael Rieves, M.D., Division Director, DMIHP  
James Moore, PharmD., M.A, Project Manager, DMIHP  
Alexander Gorovets, M.D., Clinical Team Leader, DMIHP  
Anthony Mucci, Ph.D., OB, Statistical Reviewer  
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB  
Barbara Stinson, D.O., Clinical Reviewer, DMIHP  
Eldon Leutzinger, Ph.D., Team Leader, Chemistry, ONDQA  
Josephine Jee, Ph.D., Chemistry Reviewer, ONDQA  
Siham Biade, Ph.D., Pharmacology/Toxicology Reviewer, DMIHP

James Moore, PharmD., M.A  
Project Manager

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/s/

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James Moore  
12/30/2008 04:56:19 PM

**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:** December 15, 2008

**TO:** James Moore, Regulatory Project Manager  
Barbara Stinson, Medical Officer  
Division of Medical Imaging and Hematology Products

**FROM:** John Lee, Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

**THROUGH:** Tejashri Purohit-Sheth, MD  
Branch Chief, Good Clinical Practice Branch II  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** NDA 21-711

**APPLICANT:** Epix Pharmaceuticals, Inc.

**DRUG:** Gadofosveset Trisodium (Vasovist)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard

**INDICATION:** For use with magnetic resonance angiography to evaluate aortoiliac occlusive disease in adults with known or suspected peripheral vascular disease

**CONSULTATION REQUEST DATE:** September 19, 2008

**DIVISION ACTION GOAL DATE:** December 24, 2008

**PDUFA DATE:** December 31, 2008

## I. BACKGROUND

### Radiographic Evaluation of Arterial Disease

In detecting arterial stenoses, X-ray angiography (XRA) produces excellent examinations but requires arterial catheterization and injections of potentially toxic contrast agents. XRA risks include vessel injury, embolism, allergic reactions, and contrast-induced nephropathy. Non-contrast magnetic resonance angiography (MRA) produces good examinations in normal blood vessels but often produces uninterpretable examinations in tortuous or diseased blood vessels. Hence, XRA is often performed following non-contrast MRA. The use of gadolinium-based contrast agents improve the interpretability of MRA but, to date, none of these contrast agents have been approved for use in conjunction with MRA in the United States.

### Product Application History

Vasovist (gadofosveset trisodium), one such gadolinium-based contrast agent, has been approved in more than 30 countries. In the US, the marketing application for Vasovist was originally submitted to the FDA in December of 2003. For approval, the FDA required the sponsor to perform a well-controlled, independent, and blinded re-read of examinations obtained in prior studies. Two key issues to be addressed in the blinded re-read were: (1) rigorous training and testing of the radiologists to standardize the reading, particularly for images deemed to be uninterpretable, and (2) statistical analysis plan, particularly for handling uninterpretable images.

### The "Blinded Re-Read Study"

As advised by the FDA, the sponsor performed a study which involved re-reading the images obtained previously under Studies MS-325-12 and MS-325-13. The blinded re-read followed extensive reader training and was performed with ongoing assessments of intra-reader variability and standardized identification and categorization of unobservable and uninterpretable vessel-segments. The results of the blinded re-read were interpreted according to a prospectively established statistical plan and definition of success.

- In previous Studies MS-325-12 and MS-325-13, adults scheduled for XRA evaluation of aorto-iliac occlusive disease (AIOD) underwent a non-contrast and a Vasovist-enhanced MRA, in addition to an XRA performed separately to serve as the reference standard. Study MS-325-12 was conducted at 39 centers in North and South America and Europe. Study MS-325-13 was conducted at 24 centers in North and South America, Europe, and Australia.
- The current study entitled "Blinded Re-read of Examinations from Phase 3 Studies MS-325-12 and MS-325-13 to Confirm the Diagnostic Performance of Vasovist in Subjects with Suspected Aortoiliac Occlusive Disease" (Blinded Re-Read Study) was conducted using the images obtained in these two previous studies. All examinations previously obtained under Studies MS-325-12 and MS-325-13 were sent to a core imaging facility to re-evaluate the following vessel-segments: infrarenal abdominal aorta, left and right common iliac artery, left and right external iliac artery, and left and right common femoral artery.
- In the current study, the blinded re-read was performed for 424 subjects (251 in MS-325-12, 173 in MS-325-13) in evaluable subjects (those with an interpretable XRA plus Vasovist-enhanced and non-contrast MRAs). The MRA images were re-read by 3 independent blinded radiologists and the results were compared to those of XRA (re-read by a separate independent group of blinded radiologists). The primary efficacy endpoint was percent stenosis in each of the seven vessel-segments. The radiologists who read the Vasovist-enhanced images were blinded to subject identity, medical history, volume of contrast agent, clinical signs and symptoms, final diagnosis, examining clinical institution, or XRA results. The blinded re-read occurred from January to March of 2008.

**II. INSPECTION RESULTS**

The Blinded Re-Read Study consisted of re-interpreting previously acquired images at a single central laboratory. In support of the current review cycle for NDA 21-711, the central laboratory was inspected to evaluate compliance with applicable good clinical practice (GCP) regulations and adherence to the "study protocol" (operating procedures specified in the *Blinded Reader Manual*) in conducting the Blinded Re-Read Study.

Clinical Study Site	Protocol Subjects	Inspection Dates	Classification	
			Field	Final
┌	Blinded Re-Read Study 424 subjects	Nov 2 - 8, 2008	NAI	pending

b(4)

NAI = no action indicated (no deviations from regulations); VAI = voluntary action indicated (no significant deviations from regulations); OAI = official action indicated (significant deviations from regulations); NA = not applicable

Classification:

Field = field investigator's initial recommendation in classifying the inspection result

Final = CDER's final classification of the inspection result

1. What was inspected:

- Scope of inspection: An evaluation of adherence to the operating procedures specified in the *Blinded Reader Manual* in interpreting MRA images, to include verification that images were interpreted at assigned time and place, and that the physical layout of the reading stations are consistent with the readers' blinded, independent functioning.
- Data verification: A comparison of the primary efficacy endpoint data reported under the current review cycle for NDA 21-711 with the data recorded in the case report forms (CRFs) generated at ┌ during the Blinded Re-Read Study.
- Subjects: Of the 424 subjects in the Blinded Re-Read Study, complete records were reviewed for 49 subjects (12%) selected at random.

b(4)

2. General observations and commentary: No deficiencies were observed and a Form FDA 483 was not issued. No discrepancies were noted between the CRF data and the data reported under this NDA during the current review cycle. Adherence to the operating procedures specified in the *Blinded Reader Manual* was noted to be excellent.

3. Assessment of data integrity: Data from the Blinded Re-Read Study appear reliable.

**III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

The inspection of ┌ during the conduct of the Blinded Re-Read Study revealed no deficiencies in complying with applicable GCP regulations or the study protocol (*Blinded Re-Read Manual*). The data generated from the Blinded Re-Read Study are considered acceptable in support of the proposed indication.

b(4)

**Note:** This Clinical Inspection Summary is based on preliminary inspection report; the final inspection report is pending as of December 15, 2008. Upon receipt and review of the final inspection report, an addendum to this clinical inspection summary will be provided if additional observations of clinical or regulatory significance are discovered.

{See appended electronic signature page}

John Lee, MD  
Good Clinical Practice Branch II  
Division of Scientific Investigations

**CONCURRENCE:**

{See appended electronic signature page}

Tejashri Purohit-Sheth, MD  
Branch Chief, Good Clinical Practice Branch II  
Division of Scientific Investigations

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/s/

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John Lee  
12/17/2008 10:54:06 AM  
MEDICAL OFFICER

Tejashri Purohit-Sheth  
12/17/2008 12:01:46 PM  
MEDICAL OFFICER

Preapproval Safety Conference between the Division of Medical Imaging and Hematology and the Office of Drug Safety, Thursday, December 11, 2008, White Oak FDA Campus, Building 22, Conference Room 1415

Subject: Vasovist (gadofosveset trisodium) NDA 21-711

**OSE Attendees:**

Robert Boucher, M.D.  
Susan Lu, PharmD.  
Janos Bacsanyi, M.D.  
Tara Turner, PharmD.  
Janet Anderson, PharmD.

**DMIHP/Other FDA Attendees:**

Rafel Rieves, M.D, Division Director, DMIHP  
Liberio Marzella, M.D., Ph.D., Clinical Team Leader, Acting Deputy Division Director, DMIHP  
Barbara Stinson, D.O. Clinical Reviewer, DMIHP  
Alexander Gorovets, M.D., Clinical Team Leader, DMIHP  
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, OCP  
Siham Biade, Ph.D., Pharmacology Toxicology Reviewer, DMIHP  
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB  
Michelle Fedowitz, M.D., Clinical Reviewer, DMIHP  
James Moore, PharmD., M.A., Project Manager, DMIHP

**Background**

This meeting was scheduled by DMIHP to discuss with OSE safety concerns that should be considered Post-Marketing.

**Discussion**

The following points were discussed during the meeting.

- (1) The need for monitoring for hypersensitivity reactions (fatal anaphylactic reactions).
- (2) The need for continuous monitoring for signs of acute renal failure/Nephrogenic Systemic Fibrosis (NSF).
- (3) QT Prolongation
- (4) The Trade Name of the product.

There was considerable discussion about QT prolongation with Vasovist and whether the Applicant should be asked to conduct further QT studies. There was a lengthy discussion of the name proposed by Epix for their gadolinium product (Vasovist). Staff members

from DMETS expressed their objection to the use of the name Vasovist. DMIHP did not share DMETS concerns about the trade name and stated that failure to accept the name at this point in the review process could delay an action on the application.

### **Summary**

Epix will not be asked to conduct additional QT studies with Vasovist. OSE will monitor for acute renal failure, NSF, hypersensitivity reactions (fatal anaphylactic reactions) post-marketing. DMIHP requested that a meeting be scheduled for December 16<sup>th</sup> or 17<sup>th</sup> to discuss the trade name issue. The Project Manager was requested to schedule the meeting.

The minutes were prepared by James Moore, Project Manager.

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

December 4, 2008

Regarding your pending NDA for Vasovist N 21-711, the reviewing clinical pharmacologist has the following request and comment.

Please provide a paragraph that summarizes your QTc studies for Vasovist. This information is missing in the clinical pharmacology section of your label.

Your Canadian label for Vasovist has extensive information (almost one page) on QT studies with Vasovist. We need a condensed version.

Please provide this information as soon as possible but no later than by noon tomorrow, Friday, December 5, 2008.

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

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/s/

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James Moore  
12/4/2008 12:56:38 PM  
CSO

November 18, 2008

Regarding your pending application for Vasovist NDA 21-711, does Epix plan to market the  
— fill size vial of the product? If so, please provide the NDC number for the product and list  
this information in the How Supplied section of the package insert.

**b(4)**

Please respond to this inquiry by COB Friday, November 21, 2008.

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

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/s/

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James Moore  
11/18/2008 08:48:18 PM  
CSO

October 16, 2008

Regarding your pending NDA 21-711 for Vasovist, please clarify whether a request for marketing exclusivity has been submitted for this pending application. If the request was submitted, please cite its location in the NDA.

If it has not been submitted do you plan to submit such a request? If it has not been submitted and you submit such a request please indicate in the request the number of years requested for exclusivity.

If you submit an exclusivity request please submit the request to NDA 21-711.

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

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

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/s/

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James Moore  
10/16/2008 02:18:25 PM  
CSO

September 23, 2008

Please confirm whether the datasets cited below are the datasets requested by Dr. Anthony Mucci when the application was submitted.

Electronic data sets: MS325Supp\_Data\_by Patient; MS325Supp\_Data\_by Vessel. The Field definitions run from \_pno through R\_CFA\_mpststn. (62 variables).

Please respond to this inquiry by COB Wednesday, September 24, 2008.

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

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/s/

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James Moore  
9/23/2008 10:28:50 AM  
CSO

IND 51,172: Pre-NDA Meeting between the Division of Medical Imaging and Radiopharmaceutical Drug Products and Epix Medical, Tuesday, May 20, 2003, 1PM-2:30PM, Parklawn Building, 3<sup>rd</sup> floor, Chesapeake Room

Epix Attendees:

Alan Carpenter, Ph.D., Executive Vice President for Research and Development  
Robert Weisskoff, Ph.D., Vice President of Business Development and Head of Imaging

b(4)

Paul Chamberlin, M.D., Associate Medical Director  
Phillip Graham, Ph.D., Executive Director of Preclinical Development  
Robert Morgan, M.S., Executive Director of Regulatory Affairs and Quality  
John Barrett, Ph.D., Senior Director Pharmacology/Toxicology  
Debra Suckney, M.P.H., Senior Regulatory Affairs Associate  
Brian Moyer, M.S., Director of Project Management and Clinical Pharmacology  
Michael Webb, Chief Executive Officer  
Stephen Knight, M.D., President and Chief Operating Officer

b(4)

FDA Attendees:

Julie Beitz, M.D., Deputy Office Director, ODEIII, HFD-103  
Sally Loewke, M.D., Deputy Division Director, HFD-160  
Brenda Gierhart, M.D., Acting Clinical Team Leader, HFD-160  
Robert Yaes, M.D., Ph.D., Clinical Reviewer, HFD-160  
Anthony Mucci, Ph.D., Biostatistics Reviewer, HFD-715  
Michael Welch, Ph.D., Team Leader Biostatistics, HFD-715  
Adebayo Lanionu, Ph.D., Team Leader Pharmacology/Toxicology, HFD-160  
Siham Biade, Ph.D., Pharmacology/Toxicology Reviewer, HFD-160  
Eldon Leutzinger, Ph.D., Team Leader, Chemistry, DNDCII, HFD-820  
David Place, Ph.D., Chemistry Reviewer, DNDCII, HFD-820  
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, HFD-870  
Gary Gensinger, Office of Information Management, HFD-140  
Roy Blay, Ph.D., Division of Scientific Investigations, HFD-46  
Vinnny Pawar, Ph.D., Microbiology Reviewer, Office of Pharmaceutical Science, HFD-805  
Kyong Kang, PharmD., Chief, Project Management Staff, HFD-160  
James Moore, R.Ph., M.A. Project Manager, HFD-160

Quynh Nguyen, PharmD., Office of Drug Safety, HFD-430  
Russell Williams, Jr., B.S., Operations Research Analyst, HFD-160  
Eric Duffy, Ph.D., Division Director, DNDCII, HFD-820

### **Introduction**

After introduction of FDA and Epix Medical personnel, the meeting began with a presentation by Epix Medical.

### **Background**

The meeting's focus was the questions provided by Epix Medical in their meeting package of April 7, 2003. FDA provided responses to Epix's questions on May 14, 2003. Epix's presentation reflects responses to FDA's fax of May 14, 2003. The Sponsor's questions appear in italics.

### **Discussion**

In opening remarks, Epix Medical stated that their plans are to submit the NDA for MS-325 in the late November timeframe. Epix stated that based on FDA's response to the question regarding early submission of sections of the NDA, no presubmissions would be provided.

- 1. Based on the proposed eNDA content, has the FDA identified any deficiencies that would prevent the Agency from filing this application for the proposed indication?*

In opening remarks, Epix stated that it was their intention to submit the entire NDA in electronic format. Epix queried FDA about which disciplines wanted a paper review copy of the NDA and FDA responded that all sought paper review copies and the only information that shouldn't be submitted in hard copy was the information detailed in FDA's fax of May 14, 2003. Epix also stated that they would schedule a demonstration of the entire eNDA early after the NDA is submitted. This will be arranged and done at the convenience of FDA. The studies in which Epix wishes to submit abbreviated study reports and synopses are MS-325-04/04A, 5, 8, 10, and 11. These studies were closed and not related to the proposed indication for the product. The synopsis report will be provided for the small studies and will include an abstract followed by all the safety data. The abbreviated report will be provided for the large studies and will include a full safety report.

Further discussion ensued as FDA asked the Sponsor to define an abbreviated study report and a synopsis report, and distinguish between these reports and a full study report. Epix responded that a full study report contains information on the efficacy of MS-325 and the other reports do not.

Epix Medical stated that the images would be provided in section 11 of the NDA submission and the training manual for the blinded readers would also be available there. Epix will provide sample images for review by FDA. Epix Medical will also provide the blinded reader training images.

5. *EPIX has previously requested two waivers: Pediatric waiver filed in S 129 on July 30, 2001 and the Environmental waiver filed in S. 160 on May 5, 2002. Are these waivers required to be included in the NDA? If yes, when can EPIX expect responses to these waivers?*

Epix Medical agreed to submit the request for the Environmental Assessment waiver in the NDA.

6. *For the ISS, EPIX is recoding AEs in all older clinical studies (pre-Phase III) to MEDDRA but preserving original COSTART terms in the clinical study reports. EPIX plans to provide a table in the eNDA to allow the reviewer to determine what terms have been recoded. Is this acceptable to FDA?*

This question generated a great deal of discussion as FDA sought to clarify with Epix Medical the coding of adverse events in their NDA. Specifically, FDA was concerned that information may be lost in the translation of terms from COSTART to MEDDRA. Epix explained and this was reiterated by FDA that MEDDRA is a very granular system and one COSTART term may register as several different MEDDRA terms.

Epix stated that MEDDRA takes verbatim terms and converts them to higher level terms for the purpose of adverse event reporting. According to Epix, the events will also be directed into System Organ Classes (SOCs) that will also help clarify the actual adverse events. Epix uses an autoencoder system with ~~some~~ software to code the adverse events seen in the trials. Though an autoencoder is used to streamline the coding process, human intervention is used to quality control the information before a final decision is made on the code/term that will be used to characterize the adverse event. A trained medical professional is used to quality control the information that is reported as an adverse event. The adverse event will be described in detail according to Epix and the actual patient complaint will be provided. FDA asked if a table showing conversion of COSTART to MEDDRA could be provided. Epix replied that this would be very difficult because of the granularity of MEDDRA and that coding conversion would not match well. According to Epix, COSTART and MEDDRA share a common dictionary. Adverse events in the ISS will be reported on three levels: verbatim terms, preferred terms, and the System Organ Classes (SOCs). When converting from COSTART to MedDRA, the largest differences in terminology exist for the high-level terms.

b(4)

FDA was concerned that multiple adverse events seen in the same patient may not be identified in the safety database. Epix assured FDA that all events observed for each patient could be found in the safety database in an adverse event table.

7. *EPIX plans to request Priority Review for MS-325. EPIX believes that this novel MRA contrast agent (currently no contrast agent has been approved for MRA) satisfied the unmet medical need of a non-invasive diagnostic procedure for angiographic assessment of vascular disease*

b(4)

*Does FDA agree that MS-325 is a candidate for Priority Review?*

FDA inquired whether safety data was collected on all patients in the X-ray angiography trials and Epix replied that safety data was collected on 85% of the patients in the Phase 3 trials and on all patients in the Phase 2 trials. Whether MS-325 will receive a priority review will be determined after submission of the NDA.

b(4)

FDA inquired about the studies that have been completed and what the results show. Epix replied that studies 12 and 13 have been completed and reports are being drafted. Studies MS325-14 & MS325-15 are being analyzed.

FDA inquired about the role of the adjudicator in the investigative process and Epix replied that the adjudicator was brought in when there was a disagreement on the presence or absence of a clinically significant stenosis or if there were questions of interpretability of the image. The adjudicator reviewed all cases when one blinded reader assessed  $\geq 50\%$  stenosis and one reader assessed  $< 50\%$  stenosis and gave an opinion of what the correct percent stenosis was. No readers read any image more than once. Electronic calipers were used to assess the percent stenosis by the blinded readers. Fiducial points were drawn and magnification was provided as needed for viewing. The percent stenosis was calculated electronically. Epix stated that all reads from blinded readers would be provided.

When asked by FDA about the intra-reader consistency, Epix responded that they did not have the blinded readers reread images to look at variability.

Epix stated that use of consensus reads for the truth standard was not considered because of potential bias. Independent blinded evaluations for the angiography would allow some

determination of reproducibility. There will be no pooling of data for the primary indication for the Phase 3 trials, but the data will be pooled for the

b(4)

All regions were assessed for rate of flow. High, medium, and low flow regions were all assessed. FDA identified that the total number of patients reported in the meeting package and the annual report were different. Epix apologized for the discrepancy and clarified that the annual report identified those patients enrolled in the studies and serial 185 identified those patients who were evaluable for safety.

FDA stated that it would be helpful if all data for a single patient could be provided in a single "row" of the SAS data set and stated that an example of the format for providing this data would be sent to Epix to assist them in preparation of the patient data.

FDA expressed its concern that Epix Medical considered fosveset a ligand and an intermediate. Epix stated that fosveset is added to the preparation [redacted] from the drug product. FDA then commented that fosveset shouldn't be designated as a [redacted]. FDA stated that fosveset can still be called an excipient, but advised Epix Medical that the word [redacted] should be deleted from the excipient designation. FDA requested that the Sponsor identify fosveset's function in the application.

b(4)

FDA inquired whether the product would be manufactured under GMPs and Epix replied that it would. FDA stated that more detail is needed about the drug manufacturing process, the drug substance, the drug product, and the production process in the NDA. Epix agreed to provide that information as requested by FDA. Epix said it plans to deliver [redacted] batches of product as the demand dictates. FDA stated that Epix Medical can set an interim specification based on a limited amount of data for MS-325. As data accumulates for subsequent batches ([redacted] batches over e.g., 3-year period), the data can be reviewed and the interim specification updated to a final specification. These batches may be approved for release through the prior approval process. FDA asked who the manufacturer of MS-325 would be and Epix replied that the manufacturer would be Mallinckrodt.

b(4)

FDA inquired about the source of the [redacted] in the drug product. Epix replied that the [redacted] component of the MS-325 drug product is [redacted] and Epix will provide this certification in the NDA.

b(4)

### **Summary**

At the completion of discussion Epix presented several slides of its investigation using MS-325 and its comparison to X-Ray angiography. When FDA asked what the data shows that has been analyzed Epix replied that MS-325 is highly safe and effective for the proposed indication.

### **Action Items**

- FDA will fax to Epix Medical a suggested format for patient data for the proposed SAS data set for the NDA submission.
- Epix Medical will clarify the definition of abbreviated, synopsis and final study report and submit an example of a synopsis and an abbreviated study report to FDA.

The meeting adjourned at 2:32PM.

The minutes were prepared by CAPT James Moore.

James Moore, R.Ph., M.A.  
Project Manager, HFD-160

Minutes Pre-NDA Meeting Epix Medical-DMIRDP May 20, 2003 IND 51,172 (MS-325)

Drafted by: JM/May 23, 2003

Dist: May 27, 2003

Edited by: SB/RW/QN/May 27, 2003/MW/AM/RY/KK/May 28, 2003

BG/June 4, 2003/KK/EL/June 6, 2003/SL/EL/June 12, 2003/JB/June 16, 2003

Revised by: JM/May 27, 28, June 4,12,16,18, 2003

Final by: JM/June 18, 2003

C:\data\my documents\ms325\preindaindustrymeeting5202003Finalmeetminsi51172.doc

**APPENDIX**  
**(Sponsor's Slides)**

22 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

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James Moore  
6/19/03 07:50:03 AM

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 21-711 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Vasovist Established/Proper Name: Gadofosveset Trisodium Dosage Form: Injection		Applicant: Agent for Applicant (if applicable):
RPM: James Moore		Division: 160
<p><b>NDA:</b> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2) Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		December 31, 2008 December 22, 2008
❖ Actions		
• Proposed action		x AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		AE-January 12, 2005, AE-November 21, 2005
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/cder/guidance/2197dft.pdf">www.fda.gov/cder/guidance/2197dft.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC	
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	
Comments: _____	
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: _____	November 19, 2008
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	x Yes
• Press Office notified of action (by OEP)	x Yes
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

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

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

Answer the following questions for each paragraph IV certification:

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

Yes       No

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

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

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

Yes       No

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

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

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

Yes       No

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

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

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

Yes       No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p>N/A</p>
<p><b>CONTENTS OF ACTION PACKAGE</b></p>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	<p>x</p>
<p><b>Officer/Employee List</b></p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p>x Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p>x Included</p>
<p><b>Action Letters</b></p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action and date AE-January 12, 2005 AE-November 21, 2005 AP-December 22, 2008</p>
<p><b>Labeling</b></p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant 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>	<p>x</p>
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	<p>N/A</p>
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use x/None</p>

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 9/5/08

<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	N/A
❖ Labels (full color carton and immediate-container labels) ( <i>write submission/communication date at upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	N/A
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	x RPM December 17, 2008 DMEDP DRISK x DDMAC September 23, 2008 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul>	x-December 19, 2008
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	NA
NDA's only: Exclusivity Summary ( <i>signed by Division Director</i> )	x Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	x No
<ul style="list-style-type: none"> <li>• This application is on the AIP                             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	x No  <input type="checkbox"/> Not an AP action
❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )	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 Requirement (PMR) Studies	x-See AP Letter
<ul style="list-style-type: none"> <li>• Outgoing communications (<i>if located elsewhere in package, state where located</i>)</li> </ul>	x
<ul style="list-style-type: none"> <li>• Incoming submissions/communications</li> </ul>	N/A
❖ Postmarketing Commitment (PMC) Studies	N/A
<ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	N/A

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

<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	
<ul style="list-style-type: none"> <li>Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)</li> </ul>	x
Internal memoranda, telecons, etc.	None
<b>❖ Minutes of Meetings</b>	
<ul style="list-style-type: none"> <li>PerRC (<i>indicate date; approvals only</i>)</li> </ul>	x November 19, 2008
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	x December 11, 2008
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date</i>)</li> </ul>	x No mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>	x May 20, 2003
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>	none
<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	
<b>❖ Advisory Committee Meeting(s)</b>	x No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available</li> </ul>	
<b>Decisional and Summary Memos</b>	
<b>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</b>	x December 22, 2008
Division Director Summary Review ( <i>indicate date for each review</i> )	x December 18, 2008
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	x None
<b>Clinical Information<sup>5</sup></b>	
<b>Clinical Reviews</b>	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	x December 18, 2008
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	x December 11, 2008
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	x None
<b>❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)</b>	x (see Clinical Review)
<b>❖ Financial Disclosure reviews(s) or location/date if addressed in another review</b> OR If no financial disclosure information was required, review/memo explaining why not	x (see Clinical Review)
<b>❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)</b>	x None
<b>❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)</b>	x Not needed
<b>❖ Risk Management</b> <ul style="list-style-type: none"> <li>Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> <li>REMS Memo (<i>indicate date</i>)</li> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> </ul>	x November 24, 2008
<b>❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)</b>	x
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
<b>❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)</b>	None

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

Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	x December 19, 2008
Statistical Team Leader Review(s) (indicate date for each review)	x December 19, 2008
Statistical Review(s) (indicate date for each review)	x December 19, 2008
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	x December 17, 2008
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	x December 15, 2008
Clinical Pharmacology review(s) (indicate date for each review)	x December 15, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	x
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	NA
• Supervisory Review(s) (indicate date for each review)	x December 18, 2008
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	x December 18, 2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	x None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	x No carc
ECAC/CAC report/memo of meeting	x None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	x December 19, 2008
• Branch Chief/Team Leader Review(s) (indicate date for each review)	x December 4, 2008
• CMC/product quality review(s) (indicate date for each review)	x December 4, 2008
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	None
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	x (See Chemistry Review)
<input type="checkbox"/> Review & FONSI (indicate date of review)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	N/A

<ul style="list-style-type: none"> <li>❖ NDAs: Methods Validation</li> </ul>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> <li>❖ Facilities Review/Inspection</li> </ul>	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i></li> </ul>	Date completed: September 2, 2008 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs:             <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i></li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

### 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 ADRA.