CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-016

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-016 SUPPL # N/A HFD # 510

Trade Name Vaprisol Injection

Generic Name conivaptan hydrochloride

Applicant Name Astellas Pharma US, Inc.

Approval Date, If Known February 28, 2007

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

N/A

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# 21-697 Vaprisol (conivaptan hydrochloride) Injection

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:

Study 087-CL-027: A 4-Day, Double-Blind, Placebo-Controlled Multicenter Study of IV YM087 (CI-1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia

Study 087-CL-071: A Randomized, Double-blind, Placebo-controlled, Doseranging Pilot Study Evaluating the Efficacy and Safety of YM087 in Patients with Decompensated Chronic Heart Failure

Study 087-CL-080: A 4-Day, Open-Label, Multicenter Study of Intravenous YM087 in Patients with Euvolemic or Hypervolemic Hyponatremia

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:

Investigation 1: Study 087-CL-027: A 4-Day, Double-Blind, Placebo-Controlled Multicenter Study of IV YM087 (CI-1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia (NDA 21-697 relied upon data from this investigation)

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

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

N/A

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

Investigation 1: Study 087-CL-027: A 4-Day, Double-Blind, Placebo-Controlled Multicenter Study of IV YM087 (CI-1025) to Assess Efficacy and Safety in Patients with Euvolemic or Hypervolemic Hyponatremia

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

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

Investigation #1		!
		!
IND # 56,813	YES ☒	! NO ☐
		! Explain:
Investigation #2		!

IND # YES ☐ ! NO ☐
! Explain:

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

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

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

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

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Jennifer Johnson
Title: Regulatory Project Manager, Division of Metabolism and Endocrinology Products

Date: March 21, 2007

Name of Office/Division Director signing form: Mary Parks, M.D.
Title: Director, Division of Metabolism and Endocrinology Products

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

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/s/

Mary Parks
3/21/2007 07:03:08 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

A/BLA #: 22-016 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: August 28, 2006 PDUFA Goal Date: February 28, 2007

HFD- 510 Trade and generic names/dosage form: Vaprisol (conivaptan hydrochloride) Injection

Applicant: Astellas Pharma US, Inc. Therapeutic Class: vasopressin receptor antagonist

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

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

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only):

Treatment of euvolemic hyponatremia in hospitalized patients (NDA 21-697)

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of hypervolemic hyponatremia in hospitalized patients

'his an orphan indication?

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

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: X Partial Waiver X Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

tudies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._0____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._5____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._6____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._18____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): January 31, 2013

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager

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

(Revised: 10/10/2006)

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/s/

Jennifer Johnson
3/6/2007 03:59:37 PM

Johnson, Jennifer

From: Clark, Nancy
Sent: Thursday, February 22, 2007 12:00 PM
To: Johnson, Jennifer
Cc: Dempsey, Mary
Subject: Vaprisol consult form for pharmacovigilance study

Hi Jennifer,
Through much discussion, it turns out that OSE (the RMP team nor DDRE) doesn't need to review anything for this so-called RMP. Therefore, we are considering the consult closed. Sorry for the confusion.

Thank you, Nancy

LCDR Nancy Clark, PharmD.
Project Manager
FDA/CDER/Office of Surveillance and Epidemiology
Division of Drug Surveillance, Research, and Communication Support (DSRCS)
10903 New Hampshire Ave, Building 22, Room 4467
Mail Stop 4447
Silver Spring, Maryland 20993
phone: 301-796-1187
fax: 301-796-9837
email: nancy.clark@fda.hhs.gov

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/s/

Jennifer Johnson
2/27/2007 03:54:09 PM
CSO

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Office of Surveillance and Epidemiology, Division of Drug Risk Evaluation (DDRE) HFD-430	**Jennifer Johnson, Regulatory Project Manager, DMEP HFD-510, WO 22, Room 3393**

	IND NO.	NDA NO	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 13, 2007		**22-016**	**NDA Resubmission (AZ)**	**August 25, 2006**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vaprisol (conivaptan hydrochloride) Injection		**Vasopressin**	**February 21, 2007**

NAME OF FIRM: **Astellas Pharma US, Inc.**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*: **Pharmacovigilance study proposal**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ SSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the proposed pharmacovigilance study, as requested by Mary Dempsey of the Risk Management Team in OSE.
This application resubmission is located in the EDR under NDA 22-016 (treatment of hypervolemic hyponatremia). The approved indication (treatment of euvolemic hyponatremia) is found under NDA 21-697. The proposed risk management plan for 22-016 is found in Attachment 4 of the complete response to the AE action.
The user fee goal date is February 28, 2007 and the planned action goal date is February 23, 2007.
Please feel free to contact me with any questions or comments.

Thanks,

Jennifer Johnson, RPM, (301) 796-2194

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jennifer Johnson
2/13/2007 02:37:06 PM

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Tuesday, February 13, 2007 2:09 PM
To: Dempsey, Mary
Cc: Johnson, Jennifer
Subject: RE: RMP consult? (NDA 22-016, Vaprisol)
Follow Up Flag: Follow up
Flag Status: Red

Thanks, Mary, for your help. Sorry to get back to you so late.
I am finishing up the consult request, but just wanted to be sure what section(s) of the NDA you wanted specifically consulted to DDRE.

Thanks much,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research, FDA
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

From: Dempsey, Mary
Sent: Wednesday, February 07, 2007 7:31 AM
To: Johnson, Jennifer
Cc: Dempsey, Mary
Subject: RE: RMP consult? (NDA 22-016, Vaprisol)

Jennifer,

The RMP Team has reviewed the sponsor 1 page RMP submission and the MO review. We agree with the MO conclusion that a RiskMAP or RMP beyond professional labeling and routine pharmcovigilance is not warranted for this product. There is no need to send a formal consult for a RMP review.

However, there is a proposed pharmacovigilance study which should be consulted to OSE-DDRE.

Hope this is helpful and please let me know if you have any questions.
MaryD

Mary Dempsey
Risk Management Program Coordinator
Office of Surveillance & Epidemiology (OSE)
FDA/CDER
301-796-0147

10903 New Hampshire Avenue

CDER Building #22, Room 4326
Silver Spring, MD 20993
Email Address: Mary.Dempsey@fda.hhs.gov

From: Johnson, Jennifer
Sent: Monday, February 05, 2007 11:25 AM
To: Dempsey, Mary
Cc: Johnson, Jennifer
Subject: RE: RMP consult? (NDA 22-016, Vaprisol)

Hi Mary,

The action goal date is 2.23.07 and the user fee goal date is 2.28.07.
Karen Mahoney's draft review is attached to this email.
Let me know if you need anything else.

Thanks!
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research, FDA
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

From: Dempsey, Mary
Sent: Friday, February 02, 2007 6:57 AM
To: Johnson, Jennifer
Subject: RE: RMP consult? (NDA 22-016, Vaprisol)

Jennifer,

Please forward me a draft copy of Karen's review.
What is the due date?

Thanks,
MaryD

Mary Dempsey
Risk Management Program Coordinator
Office of Surveillance & Epidemiology (OSE)
FDA/CDER
301-796-0147

10903 New Hampshire Avenue
CDER Building #22, Room 4326
Silver Spring, MD 20993
Email Address: Mary.Dempsey@fda.hhs.gov

From: Johnson, Jennifer
Sent: Thursday, February 01, 2007 6:21 PM
To: Dempsey, Mary
Cc: Johnson, Jennifer
Subject: RMP consult? (NDA 22-016, Vaprisol)

Hi Mary,

I am the PM for the Vaprisol resubmission to an AE action on December 29, 2005, NDA 22-016, which came in August 25, 2006.
Please view the attached, and let me know if you think that the risk management plan needs an official consult to your group. Astellas addressed the RMP in this brief one page. Karen Mahoney, the medical officer on this one, addressed the RMP in her review.
I apologize for not contacting you about this one sooner.

Thanks for your help,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research, FDA
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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/s/

Jennifer Johnson
2/27/2007 03:42:00 PM
CSO

Johnson, Jennifer

From: Vij, Kanika
Sent: Friday, February 16, 2007 8:44 AM
To: Johnson, Jennifer
Subject: DDMAC Vaprisol Label Review
Attachments: DDMAC Vaprisol Label Review.doc

Hello Jennifer,

I have been able to complete my review of the Vaprisol label so that you can have it prior to your labeling meeting today. My review is complete for this and, again, I'm sorry that I'll be unable to attend the meeting today.

Thanks,
Kanika

DDMAC

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-016

Astellas Pharma US, Inc.
Attention: Donald L. Raineri, Pharm.D.
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Dr. Raineri:

We acknowledge receipt on August 28, 2006 of your August 25, 2006 resubmission to your new drug application for Vaprisol© (conivaptan hydrochloride) Injection.

We consider this a complete, class 2 response to our December 29, 2005 action letter. Therefore, the user fee goal date is February 28, 2007.

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. The same decision regarding waiver/deferral made for the original NDA 21-697 will apply to this application. We are waiving pediatric studies in patients aged 0 to 5 years, and deferring studies in patients aged 6 to 18 years. Please provide a date by which these studies can be completed, if this NDA is approved.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jennifer Johnson
10/10/2006 01:08:38 PM

Johnson, Jennifer

From: Choudhury, Japobrata
Sent: Monday, February 12, 2007 10:52 AM
To: Mahoney, Karen M (CDER/DMEDP)
Sahlroot, Jon T; Johnson, Jennifer
Subject: RE: Vaprisol labeling

Todd and Jennifer,

So, there is no need of stat being in the 2-14 meeting! Japo

From: Mahoney, Karen M (CDER/DMEDP)
Sent: Monday, February 12, 2007 10:17 AM
To: Choudhury, Japobrata
Cc: Sahlroot, Jon T; Mahoney, Karen M (CDER/DMEDP)
Subject: RE: Vaprisol labeling

Hi, Japo-
The last time I heard, there was no statistical reviewer assigned to the current Vaprisol NDA (22016-000) for hypervolemic hyponatremia. I muddled through as best I could; I didn't ask for anything.
Thanks- Karen

Karen Murry Mahoney, MD, FACE
Medical Officer
FDA HFD-510
Division of Metabolism and Endocrinology Products
10903 New Hampshire Ave, Bldg 22, Room 3112
Silver Spring, MD 20993
301-796-2290
karen.mahoney@fda.hhs,gov

From: Choudhury, Japobrata
Sent: Monday, February 12, 2007 9:52 AM
To: Mahoney, Karen M (CDER/DMEDP)
Cc: Sahlroot, Jon T
Subject: Vaprisol labeling

Hi Karen!

I am under exceptional pressure for the last 12 days, working 11 to 12 hours a day. Now the turn is for Vaprisol along with QT reports. Irrespective of how much of help I ultimately become, I try to do my duties as best as I can within the available time.

Unless there were submissions from the sponsor for the third time, I thought it was over. After the 2nd submission, I had some interaction with you. During the wrap-up, I attended the first meeting and found that I had nothing to contribute. I saw you and Drs. Parks and Meyer working hard (I assumed on it) in December. So, what are we dealing with now?

Without having a goal, I do not know what to do. Kindly let me know what to read and look for. Thanks. Japo

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-016

Astellas Pharma US, Inc.
Attention: Donald L. Raineri, Pharm.D.
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Dr. Raineri:

Please refer to your New Drug Application (NDA) 22-016 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vaprisol (conivaptan hydrochloride) Injection.

We also refer to the meeting between representatives of your firm and the FDA on May 3, 2006. The purpose of the meeting was to discuss cardiac safety of Vaprisol Injection in patients with hypervolemic hyponatremia.

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

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from End of Review Conference held on May 3, 2006

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	Wednesday, May 3, 2006
TIME:	3:00 to 3:30 pm
LOCATION:	White Oak Campus
APPLICATION:	NDA 22-016
DRUG NAME:	Vaprisol (conivaptan hydrochloride) Injection
TYPE OF MEETING:	End of Review Conference

MEETING CHAIR: Mary Parks, M.D.

MEETING RECORDER: Lina AlJuburi and Jennifer Johnson

FDA ATTENDEES: (Title and Office/Division)

Curtis Rosebraugh, M.D.	Deputy Director, Office of New Drugs II
Mary Parks, M.D.	Acting Director, Division of Metabolism and Endocrinology Products (DMEP)
Theresa Kehoe, M.D.	Acting Clinical Team Leader
Karen Mahoney, M.D.	Clinical Reviewer
Hylton Joffe, M.D.	Clinical Reviewer
Jennifer Johnson	Regulatory Project Manager
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Motonori Aoki, Ph.D.	Assistant Director, Project Management
Abhijit Bare, MD, Ph.D.	Medical Director
Weizhong He, Ph.D.	Manager, Biostatistics
Todd Johnson	Manager, Clinical Studies
Sef Kurstjens,MD, Ph.D.	Senior Vice President, Research & Development
Marcia Marconi	Vice President, Regulatory Affairs, Quality & Safety
Donald Raineri, Pharm.D.	Senior Director, Regulatory Affairs
Patricia Barsanti	Regulatory Consultant

BACKGROUND:

On January 30, 2004, Yamanouchi Pharma America, Inc. submitted NDA 21-697 for Vaprisol (conivaptan HCl) Injection (YM087; 5 mg/mL, 4 mL per ampule). This new molecular entity is dual antagonist of arginine vasopressin (AVP) V_{1A} and V_2 receptors. The application was submitted with two proposed indications:

1. treatment of euvolemic hyponatremia in hospitalized patients and
2. treatment of hypervolemic hyponatremia in hospitalized patients.

On November 30, 2004, an approvable letter was issued. The deficiencies included clinical, clinical pharmacology and biopharmaceutics, and chemistry. The NDA sponsorship was later transferred from Yamanouchi Pharma America, Inc. to Astellas Pharma US. On June 30, 2005, Astellas Pharma US submitted a complete response to the November 30, 2004, approvable letter.

Review of the application, as amended, yielded the decision to take an approval action for the use of conivaptan hydrochloride in euvolemic hyponatremia in hospitalized patients. However, an approvable action was issued for the use of conivaptan hydrochloride in hypervolemic hyponatremia in hospitalized patients. Two different actions for the same application necessitated an administrative split of the application.

NDA 21-697 holds the approved indication: treatment of euvolemic hyponatremia in hospitalized patients. Approved on December 29, 2006.

NDA 22-016 holds the approvable indication: treatment of hypervolemic hyponatremia in hospitalized patients. The deficiency outlined in the approvable letter dated December 29, 2006 is as follows:

The data submitted to date reveal an imbalance in cardiac-related adverse events in patients with underlying congestive heart failure treated with conivaptan hydrochloride that may signal an unacceptable risk for conivaptan hydrochloride use for this indication. While conivaptan hydrochloride administration effectively increased serum sodium in these patients, there is concern that the benefits of correcting hyponatremia will be offset by an increased occurrence of cardiac failure events and mortality. Because the hypervolemic hyponatremia population was comprised predominantly of patients with congestive heart failure, the safety of Vaprisol for the treatment of hypervolemic hyponatremia has not been established. Additional clinical trial data addressing risk versus benefit in patients with underlying congestive heart failure are therefore needed, augmented by additional data in hypervolemic hyponatremia patients without underlying congestive heart failure.

This End of Review Conference was requested on February 3, 2006. The meeting briefing document was submitted on March 31, 2006.

b(4)

MEETING OBJECTIVES:

To discuss the use of Vaprisol (conivaptan hydrochloride) Injection for the treatment of hypervolemic hyponatremia in hospitalized patients.

DISCUSSION POINTS:
The Sponsor requested responses to the following questions. The questions are repeated below and the responses are bolded.

28 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

MEMORANDUM

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

DATE: December 23, 2005

TO: NDA Files

FROM: Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products

SUBJECT: **NDA Administrative Split**
NDA 21-697 and 22-016
Vaprisol (conivaptan hydrochloride) Injection

Background

On January 30, 2004, Yamanouchi Pharma America, Inc. submitted NDA 21-697 for Vaprisol (conivaptan HCl) Injection (YM087; 5 mg/mL, 4 mL per ampule). This new molecular entity is dual antagonist of arginine vasopressin (AVP) V_{1A} and V_2 receptors. The application was submitted with two proposed indications:

1. treatment of euvolemic hyponatremia in hospitalized patients and
2. treatment of hypervolemic hyponatremia in hospitalized patients.

On November 30, 2004, an approvable letter was issued. The deficiencies included clinical, clinical pharmacology and biopharmaceutics, and chemistry. The NDA sponsorship was later transferred from Yamanouchi Pharma America, Inc. to Astellas Pharma US. On June 30, 2005, Astellas Pharma US submitted a complete response to the November 30, 2004, approvable letter.

Administrative Split

Review of the application, as amended, yielded the decision to take an approval (AP) action for use of conivaptan hydrochloride in euvolemic hyponatremia in hospitalized patients. However, an approvable (AE) action will be taken for the use of conivaptan hydrochloride in hypervolemic hyponatremia in hospitalized patients. Two different actions for the same application necessitated an administrative split of the application.

NDA 21-697 holds the approved indication: treatment of euvolemic hyponatremia in hospitalized patients.

NDA 22-016 holds the approvable indication: treatment of hypervolemic hyponatremia in hospitalized patients. The data submitted to date reveal an imbalance in cardiac-related adverse

events in patients with underlying congestive heart failure treated with conivaptan hydrochloride that may signal an unacceptable risk for conivaptan hydrochloride use for this indication. While conivaptan hydrochloride administration effectively increased serum sodium in these patients, there is concern that the benefits of correcting hyponatremia will be offset by an increased occurrence of cardiac failure events and mortality. Because the hypervolemic hyponatremia population was comprised predominantly of patients with congestive heart failure, the safety of Vaprisol for the treatment of hypervolemic hyponatremia has not been established. Additional clinical trial data addressing risk versus benefit in patients with underlying congestive heart failure are therefore needed, augmented by additional data in hypervolemic hyponatremia patients without underlying congestive heart failure.

An approval action is planned before January 1, 2006, for NDA 21-697.

An approvable action is planned before January 1, 2006, for NDA 22-016.

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/s/

Lina Aljuburi
12/23/2005 03:34:07 PM
CSO

ACTION PACKAGE CHECKLIST

Application Information			
NDA # 22-016	NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A	
Drug: Vaprisol (conivaptan hydrochloride) Injection		Applicant: Astellas Pharma US, Inc.	
RPM: Jennifer Johnson		Division: DMEP, HFD-510	Phone # 301-796-2194

NDAs: NDA Application Type: (X) 505(b)(1) ( ) 505(b)(2) Efficacy Supplement: ( ) 505(b)(1) ( ) 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ( ) If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ( ) Confirmed ( ) Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	February 28, 2007
❖ Actions	
• Proposed action	(X) AP ( ) TA ( )AE ( ) NA ( ) CR
• Previous actions *(specify type and date for each action taken)*	AE on November 30, 2004 (under NDA 21-697) AE on December 29, 2005
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	(X) Requested in AP letter ( ) Received and reviewed

Application Characteristics

Review priority: **(X)** Standard ( ) Priority
Chemical classification (new NDAs only): 6

NDAs, BLAs and Supplements:
( ) Fast Track
( ) Rolling Review
( ) CMA Pilot 1
( ) CMA Pilot 2

( ) Orphan drug designation

NDAs: Subpart H
( ) Accelerated approval (21 CFR 314.510)
( ) Restricted distribution (21 CFR 314.520)
Subpart I
( ) Approval based on animal studies

BLAs: Subpart E
( ) Accelerated approval (21 CFR 601.41)
( ) Restricted distribution (21 CFR 601.42)
Subpart H
( ) Approval based on animal studies

NDAs and NDA Supplements:
( ) OTC drug

Other:

Other comments:

Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	( ) Yes ( ) No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	( ) Yes ( ) Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	( ) Yes **(X)** No
• Press Office notified of action	**(X)** Yes ( ) No
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) FDA Press Release ( ) FDA Talk Paper ( ) CDER Q&As ( ) Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	March 21, 2007
• Is approval of this application blocked by any type of exclusivity?	(X) No ( ) Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	(X) No ( ) Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	( ) No (X) Yes If yes, NDA # 21-697 and date exclusivity expires: 12/29/2010
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	(X) No ( ) Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	(X) No ( ) Yes If yes, NDA # and date exclusivity expires:
Patent Information (NDAs and NDA supplements only)	
• 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.	**(X)** Verified ( ) Not applicable because drug is an old antibiotic.
• 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.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [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).	( ) N/A (No paragraph III certification) Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	

(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (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).*	() Yes () No
(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)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (3).*	() Yes () No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (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.*	() Yes () No
(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)? *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).*	() Yes () No
(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? (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	() Yes () No

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). *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*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Clinical Team Leader Memo February 26, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	February 27, 2007
• Original applicant-proposed labeling	January 30, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Patient Package Insert (None)	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide (None)	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	AP December 29, 2005 (under NDA 21-697)
• Most recent applicant-proposed labeling	AP December 29, 2005 (under NDA 21-697)

Clinical Information	
Clinical review(s) *(indicate date for each review)*	February 2, 2007 December 7, 2005 (see 21-697) November 16, 2004 (see 21-697)
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	See page 10 of clinical review
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	Division of Cardio-Renal Products December 18, 2006
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	N/A
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	See page 6 of clinical review
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	None needed
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	N/A
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	(X) None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	October 14, 2004 (see 21-697)
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	December 18, 2006 December 8, 2005 (see 21-697) October 6, 2004 (see 21-697)

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	(X) DMETS December 1, 2005 ( ) DSRCS (X) DDMAC February 16, 2007 ( ) SEALD ( ) Other reviews ( ) Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	None
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	March 21, 2007
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	 N/A N/A
❖ Pediatric Page (all actions)	(X) Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	(X) Verified, statement is acceptable (refer to NDA 21-697)
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	Yes, PREA only (please refer to AP letter)
• Incoming submission documenting commitment	March 5, 2007
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	March 6, April 28, May 30, July 12, October 10, November 29, 2006; January 19, January 29, February 20, February 23, February 26, and February 27, 2007
❖ Memoranda and Telecons, etc.	None
❖ Minutes of Meetings (also refer to both review cycles of NDA 21-697 and NDA 22-016)	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	August 6, 2003
• EOP2 meeting *(indicate date)*	January 30, 2001
• Other (e.g., EOP2a, CMC pilot programs): End of Review Conference	May 3, 2006
❖ Advisory Committee Meeting	(X) No AC meeting
• Date of Meeting	N/A
• 48-hour alert or minutes, if available	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	December 5, 2005 (see 21-697)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	( ) None **Microbiology**
BLAs: Product subject to lot release (APs only)	( ) Yes ( ) No
Environmental Assessment (check one) (original and supplemental applications)	
• (X) Categorical Exclusion *(indicate review date)(all original applications and*	October 26, 2004 (see 21-697)

all efficacy supplements that could increase the patient population)	
• ☐ Review & FONSI *(indicate date of review)*	N/A
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	June 2, 2004 (see NDA 21-697)
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: November 23, 2004 (see 21-697) **(X)** Acceptable **( )** Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	N/A ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	**(X)** Completed (see 21-697) **( )** Requested **( )** Not yet requested **( )** Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	September 22, 2004 (see 21-697)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	N/A
Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	May 27, 2004 (see 21-697)
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	N/A

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/s/

Jennifer Johnson
3/22/2007 01:00:46 PM