CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-643

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

AstraZeneca LP
1800 Concord Pike
Wilmington, DE 19850-5437

M.V.I. Adult™ (Multi-Vitamins for Infusion)
NDA 21-643

PATENT INFORMATION ON ANY PATENT THAT CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

DECLARATION

Pursuant to 21 CFR Section 314.53(c)(3), the Applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product which is the subject of this new drug application.

GEORGE A. GILBERT

AstraZeneca Pharmaceuticals LP
M.V.I. Adult™ (Multi-vitamin for Infusion)

PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

For further information regarding this section, please contact:

Matthew E. Arnold
Regulatory Project Manager
(302) 886-3303
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

AstraZeneca Pharmaceuticals LP
M.V.I. Adult™ (Multi-vitamin for Infusion)

PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

This section not applicable to this application

For further information regarding this section, please contact:

Matthew E. Arnold
Regulatory Project Manager
(302) 886-3303
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

M.V.I. Adult is a trademark, the property of aaiPharma.

EXCLUSIVITY SUMMARY for NDA # 21-643 SUPPL #

Trade Name M.V.I. Adult Pharmacy Bulk Package (PBP)

Generic Name Multi-vitamin infusion (PBP)

Applicant Name aaiPharma Agent: Astra Zeneca HFD- 510

Approval Date February 17, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

      If yes, what type(SE1, SE2, etc.)?

   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 / X /

      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.

This application consists of Microbiology and Chemistry information, and labeling. All clinical data is incorporated by reference to the existing adult multivitamin product, M.V.I.12 (NDA 8-809), approved February 20, 1953, or the Adult multivitamin product, M.V.I. Adult (NDA 21-625), approved January 30, 2004.

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 /__X__/

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

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

YES /___/ NO /__X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /__X__/ NO /___/

If yes, NDA # N 21-625 Drug Name M.V.I. Adult

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /__X__/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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 /___/
Investigation #3	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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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 #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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

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

Investigation #1 IND # _____ YES /___/	NO /___/ Explain:
Investigation #2 IND # _____ YES /___/	NO /___/ Explain:

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

Investigation #1 YES /___/ Explain _____ _____ _____	NO /___/ Explain _____ _____ _____
Investigation #2 YES /___/ Explain _____ _____ _____	NO /___/ Explain _____ _____ _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

(See appended electronic signature page)

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

(See appended electronic signature page)

David G. Orloff, MD
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi
Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

DRAFT 02/02/04

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-643 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: April 18, 2003 Action Date: TBD

HFD 510 Trade and generic names/dosage form: M.V.I. Adult Pharmacy Bulk Package (Multi-vitamin for infusion)

Applicant: aaiPharma Agent: AstraZeneca Therapeutic Class:

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: This is an adult formulation of multivitamins for infusion Pharmacy Bulk Package

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

☒ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

tion 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: A pediatric multivitamin product, M.V.I. Pediatric (NDA 18-920) was approved April 6, 1983.

If studies 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:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ 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
☐ 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

nplete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ 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
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): _____

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:

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}

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Endocrine and Metabolic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

aaiPharma™
EVELOPING CHEMISTRY INTO MEDICINE

2320 Scientific Park Drive
Wilmington, NC 28405

Phone: 1.910.254.7000
Fax: 1.910.815.2387
1.800.575.4224

December 19, 2003

Debarment Certification

Dr. David G. Orloff, Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II, HFD-510
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane, Rm 14B19
Rockville, Maryland 20857

RE: Debarment Certification
NDA 21-643

Dear Dr. Orloff;

In accordance with the requirement Section 306(k) of the Federal Food Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, aaiPharma Inc. hereby certifies that *aaiPharma* did not and will not use in any capacity the services of any person debarred under Section 306 of the Act in connection with the development of this New Drug Application for M.V.I. Adult (multi-vitamin infusion).

Sincerely

Wayne L. Whittingham
Senior Director, Regulatory Affairs

AstraZeneca Pharmaceuticals LP
M.V.I. Adult™ (Multi-vitamin for Infusion)

FINANCIAL DISCLOSURE FROM CLINICAL INVESTIGATORS

This section not applicable to this application. There is no new clinical data presented herein.

For further information regarding this section, please contact:

Matthew E. Arnold
Regulatory Project Manager
(302) 886-3303
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

to EDR 2/12/04

AstraZeneca

Date: FEB 0 9 2004

Central Document Room
Attn: David G. Orloff, M.D., Director,
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

RE: NDA 21-643
M.V.I. Adult™ (Multi-vitamin Infusion)[Pharmacy Bulk Package]
Response to February 2, 2004 Email

Dear Sir/Madam:

Reference is made to the February 2, 2004 email from Ms. Holly Wieland of the Division of Metabolic and Endocrine Drug Products to Mr. Matthew Arnold of AstraZeneca LP (AstraZeneca). This email contained labeling comments on the proposed labeling for the above referenced application. This submission contains a complete response to the February 2, 2004 email.

AstraZeneca has made the requested changes as presented in the February 2, 2004 email. Accordingly, please find on the enclosed CD-ROM, revised labeling incorporating the requested change for the package insert. Please note that no changes to the Vial labels nor the carton were required in order to comply with the Agency's comments. They are however included on the enclosed CD-ROM for your ease of review.

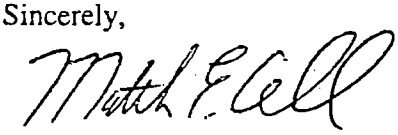
The aforementioned CD-ROM containing the labeling has been scanned using Symantec Antivirus, Version 8.00 (Corporate Edition) with a virus definition list dated February 4, 2004. No viruses were detected and AstraZeneca certifies that the CD-ROM is virus-free. The package insert is provided as a Word 2000 file and as a .pdf file.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Please direct any questions or requests for additional information to me, or in my absence, to Judy Firor, Regulatory Affairs Director, at (302) 886-7539.

Sincerely,



Matthew E. Arnold
Regulatory Project Manager
Telephone: (302) 886-3303
Fax: (302) 886-2822

MEA

cc: aaiPharma
Attn: Wayne Whittingham, Senior Director, Regulatory Affairs
2320 Scientific Park Drive
Wilmington, NC 28405

Ms. Holly Wieland, Consumer Safety Officer, HFD-510 (Cover Letter Only)

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

2 § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-_____

AstraZeneca

Date: DEC 2 2 2003

David G. Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19, HFD-510
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-643
M.V.I. Adult™ (Multi-vitamin Infusion) [Pharmacy Bulk Package]
Amendment to New Drug Application

Dear Dr. Orloff:

Reference is made to the New Drug Application (NDA 21-643) for M.V.I. Adult™ (Multi-vitamin Infusion) submitted to the Agency on April 17, 2003. This application contain the reformulation of M.V.I.®-12 (Multi-vitamin Infusion), NDA 8-809, in compliance with the Federal Register (FR) Notices of September 17, 1984 (49 FR 36446) and of April 20, 2000 (65 FR 21200).

Enclosed please find a revised Debarment Certification from aaiPharma, the applicant for this application. This Certification replaces the one found in the original NDA submission (Volume 1.1 Page 7). Note that the Debarment Certification from the U.S. Agent, AstraZeneca LP, found in the original NDA submission (Volume 1.1 Page 6) is still valid.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Please direct any questions or requests for additional information to me, or in my absence, to Judy Firor, Regulatory Affairs Director, at (302) 886-7539.

Sincerely,

Matthew E. Arnold
Regulatory Project Manager
Telephone: (302) 886-3303
Fax: (302) 886-2822

MEA

cc: aaiPharma
Attn: Wayne Whittingham, Senior Director, Regulatory Affairs
2320 Scientific Park Drive
Wilmington, NC 28405

Ms. Enid Galliers, Chief, Project Management Staff, HFD-510

Ms. Holly Wieland, Consumer Safety Officer, HFD-510

AstraZeneca

Date: NOV 1 1 2003

Central Document Room
Attn: David G. Orloff, M.D., Director,
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 21-643
M.V.I. Adult™ (Multi-vitamin for Infusion)[Pharmacy Bulk Package]
Response to Request for Information

Dear Sir/Madam:

Reference is made to the New Drug Applications (NDA 21-625 and NDA 21-643) for M.V.I. Adult™ (Multi-vitamin for Infusion) submitted to the Agency on February 27, 2003 and April 17, 2003, respectively. These applications contain the reformulation of M.V.I.®-12 (Multi-vitamin for Infusion), NDA 8-809, in compliance with the Federal Register (FR) Notices of September 17, 1984 (49 FR 36446) and of April 20, 2000 (65 FR 21200).

Reference is also made to telephone conversations between Dr. David Lewis of the Division of Metabolic and Endocrine Drug Products and Matthew Arnold of AstraZeneca LP (AstraZeneca) on August 14, 2003, August 18, 2003, and September 25, 2003.

In the August 14, 2003 and August 18, 2003 emails, Dr. Lewis requested that the following be provided: (1) the location where the Bacterial Endotoxin Testing is performed; (2) the Vitamin K specification from NDA 18-920, M.V.I.® Pediatric; (3) clarification as to the method used for Bacterial Endotoxin Testing; and (4) the FDA approval status of the [redacted] stopper indicated in the NDA as being used for the single dose configuration present in NDA 21-625.

In the September 25, 2003 email, Dr. Lewis identified some apparent discrepancies between the container/closure descriptions provided in the May 12, 2003 submission to NDA 21-643 for the Pharmacy Bulk Package. Specifically these observations were around the size of the vials and the instructions contained in the Package Insert for use of the product.

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

In accord with Dr. Lewis' request, please find the following information:

Bacterial Endotoxin Testing

The Bacterial Endoxin Testing is performed at the same locations as that currently approved in NDA 8-809, M.V.I.-12® and as stated in the April 17, 2003 Amendment to NDA 21-625 and the original NDA 21-643 submission of April 17, 2003. For your convenience, this information is further clarified below:

NDA 21-625

- The [redacted] Testing for the single dose configuration is performed by AstraZeneca LP (Westborough, MA).
- The [redacted] Testing for the unit dose configuration is performed by Enzon, formerly Elan (Indianapolis, IN).

NDA 21-643

- The [redacted] Testing for the Pharmacy Bulk Package is performed by AstraZeneca LP (Westborough, MA).

Vitamin K Specification

The vitamin K specification proposed in these applications (Original NDA 21-625 February 27, 2003, Vol. 2-pg. 13; Original NDA 21-643 April 17, 2003, Vol. 1-pg. 22) are the same as that approved in NDA 18-920, M.V.I.® Pediatric. The current Vitamin K (phytonadione) specifications from NDA 18-920, M.V.I.® Pediatric, are contained herein as **Attachment 1.**

Method Used for Bacterial Endotoxin Testing

As stated above, the Bacterial Endotoxin Testing for the single dose configuration and Pharmacy Bulk Package is performed by AstraZeneca LP and for the unit dose configuration by Enzon. The analytical methods utilized by AstraZeneca are [redacted] and the method utilized by Enzon is [redacted] For your ease of review, the proposed product specifications and list of analytical method numbers for NDA 21-625 are contained herein as **Attachment 2** and for NDA 21-643 as **Attachment 3.**

FDA Approval Status of the [redacted] Stopper

Dr. Lewis indicated that AstraZeneca stated the packaging components proposed for MVI Adult are the same as that currently approved in M.V.I.-12®, NDA 8-809 and that a [redacted] Stopper [redacted] is specified for use in the single dose configuration in NDA 21-625. Dr. Lewis indicated that he had no record of this particular stopper being approved for use for NDA 8-809, only a [redacted] stopper which was a replacement for a [redacted] stopper. (Approved March 30, 1998)

The [redacted] Stopper was submitted to NDA 8-809 a[redacted] and approved on December 7, 1990.

Vial Size and Labeling Instructions

Dr. Lewis identified some apparent discrepancies between the container/closure descriptions for the Pharmacy Bulk Package (NDA 21-643), specifically around the description of the size of the vials and the instructions contained in the Package Insert for use of the product. The product is

vial, both of which contain 50 mL of fill. Dr. Lewis indicated that he did not feel this information is clearly stated on the proposed labeling (vial labels, carton, and package insert). Therefore,

that M.V.I. Adult™ (Pharmacy Bulk Package) is

and

Based on Dr. Lewis' comments, an internal review of all of the labeling submitted to NDA 21-625 and NDA 21-643 was subsequently conducted with one additional error observed. It was found that the store upright requirement was inadvertently left off the carton for the unit dose configuration (NDA 21-625). Therefore, we are providing a revised carton reflecting this storage requirement.

Accordingly, please find on the enclosed CD-ROM, revised labeling incorporating the aforementioned changes for Vial 1, Vial 2, carton, and package insert for the Pharmacy Bulk Package (NDA 21-643) and the carton for the unit dose (NDA 21-625) in **Attachment 4.**

The aforementioned CD-ROM containing the labeling has been scanned using Symantec Antivirus, Version 8.00 (Corporate Edition) with a virus definition list dated October 24, 2003. No viruses were detected and AstraZeneca certifies that the CD-ROM is virus-free. The package insert is provided as a Word 2000 file and as a .pdf file.

Stability Data

The stability data is now available for these applications. Accordingly, please find enclosed the cumulative stability data for NDA 21-625 in **Attachment 5** and for NDA 21-643 in **Attachment 6.**

Vitamin D and Vitamin K Analytical Method

An updated version of the Vitamin D and K method is provided. The chromatographic conditions of the method have been updated in order to specify the need to equilibrate samples prior to analysis and to revise temperature. The calculations section has been revised

to only use peak height response for quantitation. These method updates are supported by the method qualification study previously provided to the agency in the submissions dated May 12, 2003 to both NDA 21-625 (Volume 3.1) and NDA 21-643 (Volume 2.1). This method is applicable to both NDA 21-625 and NDA 21-643 and is contained herein as **Attachment 7**.

As the authorized US agent, AstraZeneca has submitted this Response to Request for Information to the Division of Metabolic and Endocrine Drug Products on behalf of the applicant, aaiPharma (formerly Neosan Pharmaceuticals).

In accordance with 21 CFR 314.50 (d)(1)(v), AstraZeneca certifies that a true copy of this Amendment to New Drug Application is simultaneously being provided to the New England District Office of the Food and Drug Administration and designated as a field copy.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Judy Firor, Regulatory Affairs Director, at (302) 886-7539.

Sincerely,

Matthew E. Arnold
Regulatory Project Manager
Telephone: (302) 886-3303
Fax: (302) 886-2822

MEA

cc: aaiPharma
Attn: Wayne Whittingham, Senior Director, Regulatory Affairs
2320 Scientific Park Drive
Wilmington, NC 28405

Dr. David Lewis, Chemist, HFD-150

Ms. Enid Galliers, Chief, Project Management Staff, HFD-510 (Cover Letter Only)

AstraZeneca

Date: JUN 0 4 2003

ORIGINAL

N-000-BC

JUN 0 5 2003

David G. Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19, HFD-510
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-643
M.V.I. Adult™ (Multi-vitamin for Infusion)[Pharmacy Bulk Package]
Amendment to Pending Application

Dear Dr. Orloff:

Reference is made to the New Drug Application (NDA 21-643) for M.V.I. Adult™ (Multi-vitamin for Infusion)[Pharmacy Bulk Package] submitted to the Agency on April 17, 2003. Additional reference is made to the May 14, 2003 FDA Information Request Letter issued to the aforementioned NDA. The May 14, 2003 letter requested the addition of testing of benzo(a)pyrene content for vitamin E raw material with a specification of NMT 1ppb. One of the options provided by the Agency in the May 14, 2003 letter as a means of fulfilling this request is to make a commitment to perform this testing.

Therefore, on behalf of aaiPharma, we commit to submit a "Changes Being Effected" (CBE-0) supplement within 6 months of approval of the NDA for performing benzo(a)pyrene content on vitamin E raw material with a specification of NMT 1ppb. (See Attachment 1)

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Please direct any questions or requests for additional information to me, or in my absence, to Judy Firor at (302) 886-7539.

Sincerely,

Matthew E. Arnold
Regulatory Project Manager
Telephone: (302) 886-3303
Fax: (302) 886-2822

MEA

cc: aaiPharma
Attn: Wayne Whittingham, Senior Director, Regulatory Affairs
2320 Scientific Park Drive
Wilmington, NC 28405

Enid Galliers, Chief, Project Management Staff, HFD-510 (Cover Letter Only)

Mamta Gautam-Basak, Chemistry Team Leader, HFD-510 (Cover Letter Only)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Ack letter
05/25/03

NDA 21-643

aaiPharma
Attention: Matthew Arnold
Regulatory Project Manager
AstraZeneca LP, Agent for aaiPharma
1800 Concord Pike
Wilmington, DE 19803-8355

Dear Mr. Arnold:

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: M.V.I. Adult (multi-vitamin for infusion) Pharmacy Bulk Package

Review Priority Classification: Standard (S)

Date of Application: April 17, 2003

Date of Receipt: April 18, 2003

Our Reference Number: NDA 21-643

As stated in our filing review letter, we will file the application on June 17, 2003, in accordance with 21 CFR 314.101(a). The user fee goal date will be February 18, 2004.

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/ Courier/ Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Enid Galliers
5/25/03 07:35:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-643

aaiPharma
Attention: Matthew Arnold
Regulatory Project Manager
AstraZeneca LP, agent for aaiPharma
1800 Concord Pike
Wilmington, DE 19803-8355

Dear Mr. Arnold:

Please refer to your April 17, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for M.V.I. Adult (multi-vitamin for infusion) Pharmacy Bulk Package.

We also refer to your submission dated May 12, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 17, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
(HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Enid Galliers
5/15/03 09:27:03 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-625
NDA 21-643

INFORMATION REQUEST LETTER

IR letter
5.14.03

aaiPharma
Attention: Kevin McKenna
Executive Director, Regulatory Affairs,
AstraZeneca, Agent for aaiPharma
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. McKenna:

Please refer to your February 27, 2003, new drug application (NDA 21-625) and your April 17, 2003, new drug application (NDA 21-643) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug products:

NDA 21-625 M.V.I. Adult (multi-vitamin for infusion) and
NDA 21-643 M.V.I. Adult (multi-vitamin for infusion) Pharmacy Bulk Package

We also refer to your submissions dated March 12 and April 17, 2003 for NDA 21-625.

We are reviewing the chemistry, manufacturing, and controls section of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDAs.

Recently, it has been reported that certain forms of natural-source vitamin E, namely d-alpha-tocopheryl, d-alpha-tocopheryl acetate (Vitamin E acetate), and d-alpha-tocopheryl succinate, may contain high contamination levels of polycyclic aromatic hydrocarbons (PAH). Among these PAH compounds, benzo(a)pyrene is considered to be mutagenic and carcinogenic in animals. To reduce the potential adverse effects of benzo(a)pyrene contamination, the Agency is implementing a new policy requiring every lot of vitamin E used in the formulation of any approved product to be tested for benzo(a)pyrene content, with an acceptance criterion of NMT 1 ppb. Since vitamin E acetate is one of ingredients used in your pending applications, M.V.I. Adult and M.V.I. Adult Pharmacy Bulk Package, the Agency is requesting that batches of vitamin E acetate used in the manufacture of your products comply with such a limit. This testing may be performed by the bulk vitamin supplier(s), as long as the results are included on the Certificate of Analysis for every batch of vitamin E acetate received. Alternatively, the test should be included as part of your acceptance testing protocol if it is not performed by the suppliers(s). Please revise your current acceptance specification to reflect such a change (i.e., the addition of a test for benzo(a)pyrene content with an acceptance criterion of NMT 1 ppb)

and submit the revised acceptance specification for Vitamin E acetate to the Agency in an amendment to your pending applications. Alternatively, you may submit - in an amendment to your pending applications - a commitment to submit a "Changes Being Effected" (CBE-0) supplement within 6 months after approval of each NDA.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Mamta Gautam-Basak, Ph.D.
Chemistry Team Leader II for the
Division of Metabolic and Endocrine Drug Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Mamta Gautam-Basak
5/14/03 04:29:57 PM

AstraZeneca

ORIGINAL

Date: MAY 1 2 2003

RECEIVED
MAY 1 3 2003
FDA/CDER

N000 (BZ)
ORIG AMENDMENT

David G. Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19, HFD-510
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-643
M.V.I. Adult™ (Multi-vitamin for Infusion)[Pharmacy Bulk Package]
Response to Request for Information

Dear Dr. Orloff:

Reference is made to the New Drug Application (NDA 21-643) for M.V.I. Adult™ (Multi-vitamin for Infusion)[Pharmacy Bulk Package] submitted to the Agency on April 17, 2003. This application contains the reformulation of M.V.I.®-12 (Multi-vitamin for Infusion), NDA 8-809, which complies with the Federal Register (FR) Notices of September 17, 1984 (49 FR 36446) and of April 20, 2000 (65 FR 21200).

Reference is also made to a telephone conversation between Dr. Vinayak (Vinnie) Pawar of your Office and Matthew Arnold of AstraZeneca LP (AstraZeneca) on April 24, 2003. Dr. Pawar acknowledged that the original NDA application referenced NDA 8-809 (MVI®-12) for both container closure and Product Filtration Validation information, however, he requested that the documentation for the container closure and Product Filtration Validation information (a summary or copies of recent reports) be submitted to this application.

In accord with Dr. Pawar's request, please find the following information:

- Primary Packaging Components Information **(TAB 1)**
- Filter Validation Studies **(TAB 2)**

Additionally, the — stability data is now available for this application. Accordingly, please find enclosed the cumulative stability data. **(TAB 3)**

Also, an updated Analytical Method Validation Report is available for Vitamin D_2 and Vitamin K_1. The Validation Report entitled "Qualification for Quantitative Determination of Ergocalciferol (Vitamin D_2) and Phytonadione (Vitamin K_1) in Reformulated MVI Adult Formulation" and the Analytical Method are enclosed. **(TAB 4)**

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

In accordance with 21 CFR 314.50 (d)(l)(v), AstraZeneca certifies that a true copy of this Response to Request for Information is simultaneously being provided to the New England District Office of the Food and Drug Administration and designated as a field copy.

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

Please direct any questions or requests for additional information to me, or in my absence, to Judy Firor at (302) 886-7539.

Sincerely,

Matthew E. Arnold
Regulatory Project Manager
Telephone: (302) 886-3303
Fax: (302) 886-2822

MEA

cc: aaiPharma
Attn: Wayne Whittingham, Senior Director, Regulatory Affairs
2320 Scientific Park Drive
Wilmington, NC 28405

Ms. Enid Galliers, Chief, Project Management Staff, HFD-510

Dr. Vinayak (Vinnie) Pawar, Microbiology Reviewer, HFD-805

AstraZeneca

Date: APR 1 7 2003

David G. Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19, HFD-510
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-643
M.V.I. Adult™ (Multi-vitamin for Infusion)[Pharmacy Bulk Package]
New Drug Application: Post-DESI

Dear Dr. Orloff:

Reference is made to the New Drug Application (NDA 21-625) for M.V.I. Adult™ (Multi-vitamin for Infusion) submitted to the Agency on February 27, 2003. This application contains the reformulation of M.V.I.®-12 (Multi-vitamin for Infusion), NDA 8-809, which complies with the Federal Register (FR) Notices of September 17, 1984 (49 FR 36446) and of April 20, 2000 (65 FR 21200).

The FR Notices called for the reformulation of parenteral multivitamin products that include modifications in the adult formulation and certain portions of the labeling. Specifically, the Notices requested increases in the amount of vitamins B_1, B_6, C, folic acid, and the addition of vitamin K to the adult formulation. Whereas the FR notices stated this submission to be made as a sNDA to the existing NDA, NDA 8-809, the Division indicated in their January 24, 2003 facsimile to aaiPharma their request for this reformulation to be submitted as a NDA. This submission is made on behalf of aaiPharma. A letter authorizing AstraZeneca to serve as the US agent is enclosed.

Additional reference is made to a telephone conversation between Ms. Enid Galliers of your Office and Matthew Arnold of AstraZeneca LP (AstraZeneca) on March 25, 2003 and a follow up conversation on March 28, 2003 which additionally included Dr. Kevin McKenna of AstraZeneca. Ms. Galliers indicated that, in accordance with the December 2000 Draft Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Purposes of Assessing User Fees, since NDA 21-625 contained multiple packaging configurations which included a Pharmacy Bulk Package, a new NDA would need to be submitted to separate the Pharmacy Bulk Package from the other configurations. Accordingly, this application is for M.V.I. Adult™ (Multi-vitamin for Infusion) [Pharmacy Bulk Package].

An agreement with Ms. Galliers was reached as to the format of this NDA. It was agreed that all information previously provided in NDA 21-625 for the Pharmacy Bulk Package would be incorporated via the provision of a comprehensive index; revised labeling would be provided which provides for the Pharmacy Bulk Package as a separate package insert; and original signature documents would also be required. This submission is formatted in accord with this agreement.

The enclosed CD-ROM containing the labeling has been scanned using Norton Antivirus, Version 7.03 (Corporate Edition) with a virus definition list dated April 9, 2003. No viruses were detected and AstraZeneca certifies that the CD-ROM is virus-free. The package insert is provided as a Word 2000 file and as a .pdf file.

Based on the stability data generated to date, we propose using the same expiry dating as that currently approved in NDA 8-809 for the existing Multi-vitamin formulation (M.V.I.®-12).

Since there is already an approved pediatric version of this product available, M.V.I. Pediatric® (NDA 18-920), no pediatric development plan is provided in this application.

In accordance with 21 CFR 314.50 (d)(l)(v), AstraZeneca certifies that a true copy of this New Drug Application is simultaneously being provided to the New England District Office of the Food and Drug Administration and designated as a field copy.

As required in Section 736 of the Federal Food, Drug and Cosmetic Act, AstraZeneca LP (AstraZeneca) on behalf of aaiPharma has provided a Prescription User Fee payment in the amount of $266,700. This represents full payment of the application fee. The User Fee ID Number for NDA 21-643 is 4531.

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

Please direct any questions or requests for additional information to me, or in my absence, to Matthew Arnold at (302) 886-3303.

Sincerely,

Kevin McKenna, Executive Director
Regulatory Affairs
Telephone: (302) 886-2742
Fax: (302) 886-2822

KM/MEA

cc: aaiPharma
Attn: Wayne Whittingham, Senior Director, Regulatory Affairs
2320 Scientific Park Drive
Wilmington, NC 28405

Ms. Enid Galliers, Chief, Project Management Staff, HFD-510

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

X § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-_____

4/10/03 $266,700

USER FEE VALIDATION SHEET

NDA # 21-643 Supp. Type & # N 000 UFID # 4531
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. YES (NO) APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES (NO) SMALL BUSINESS EXEMPTION

4. YES (NO) WAIVER GRANTED

5. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division	NDA #
N_____	HFD-_____	N_____	HFD-_____	N_____

7. P (S) PRIORITY or STANDARD APPLICATION?

PM Signature / Date
2/14/00

CPMS Concurrence Signature / Date
Edd Gallies 4/28/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-643	Efficacy Supplement Type SE-	Supplement Number	
Drug: M.V.I. Adult PBP		Applicant: aaiPHARMA	
RPM: Holly Wieland		HFD- 510	Phone # 301-827-6410
Application Type: ( ) 505(b)(1) (X) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	NA
❖ User Fee Goal Dates	February 18, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	February 2, 2004
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Filing Review May 15, 2003
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(*) Materials requested in AP letter * NOT APPLICABLE ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (NA) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	February ~~17~~ 9, 2004
• Original applicant-proposed labeling	April 17, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	February 17, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	April 17, November 11, 2003; February 9, ~~17~~, 2004
• Reviews	February 17, 2004
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Consult request April 28, 2003; IR letter May 14, 2003; Filing Review letter May 15, 2003; ack letter May 25, 2003; IR email February 2, 2004
❖ Memoranda and Telecons	April 17, May 12, June 4, November 11, and December 22, 2003
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA

• Other	NA
Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	FR Notices September 17, 1984 (49 FR 36446) and April 20, 2000 (65 FR 21200)
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	NA
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	NA
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	NA
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	February 2, 2004
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	NA
❖ Biopharmaceutical review(s) *(indicate date for each review)*	NA
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	February 13, 2004
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	February 13, 2004
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	February 13, 2004
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	August 27, 2003
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	NA
❖ Nonclinical inspection review summary	NA
Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
CAC/ECAC report	NA