

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-625

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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

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

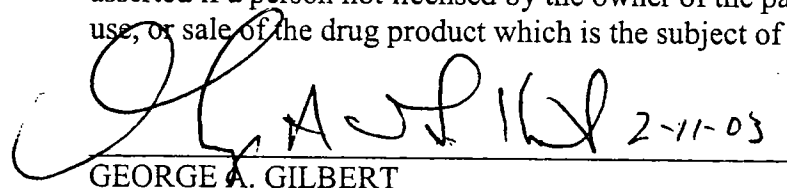
AstraZeneca LP
1800 Concord Pike
Wilmington, DE 19850-5437

M.V.I. Adult™ (Multi-Vitamins for Infusion)
NDA 21-625

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.

 2-11-03

GEORGE A. GILBERT

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 # 21-625 SUPPL #
Trade Name M.V.I. Adult Generic Name Multi-vitamin Infusion

Applicant Name aaiPharma (Agent: Astra Zeneca) HFD- 510

Approval Date: January 30, 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 only CMC 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 pediatric multivitamin product, M.V.I. Pediatric (NDA 18-920), approved April 6, 1983.

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 21-163 Drug Name INFUVITE 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 /___/

*Appears This Way
On Original*

*Appears This Way
On Original*

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: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 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

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

/s/

Mary Parks
2/2/04 10:28:23 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-625 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: February 27, 2003 Action Date: January 30, 2004

HFD 510 Trade and generic names/dosage form: M.V.I. Adult (Multi-vitamin 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 a daily multivitamin maintenance dosage for adults and children aged 11 and above.

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.

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: 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 complete 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.

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

This page was completed by:

{See appended electronic signature page}

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

NDA 21-625

Page 3

cc: NDA

HFD-960/ Grace Carmouze

(revised 10-14-03)

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

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

/s/

Holly Wieland
2/2/04 12:25:11 PM

aaiPharmaTM
VELOPING 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 21-625**

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 subsection (a) or (b) of the Act in connection with the development of this New Drug Application for M.V.I. Adult (multi-vitamin infusion).

Sincerely

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

DEBARMENT CERTIFICATION

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

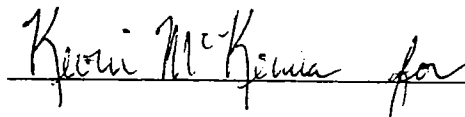
M.V.I. Adult is a trademark, the property of aaiPharma.

ITEM 16 DEBARMENT CERTIFICATION

16.0 Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca LP (AstraZeneca), that we did not use and will not use in connection with this New Drug Application for M.V.I. Adult™ (Multi-vitamin for Infusion), the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

 _____ for

Anthony Rogers, Vice President
Regulatory Affairs
AstraZeneca

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

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



12-11-03

NDA 21-625

DISCIPLINE REVIEW LETTER

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 February 27, 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 infusion).

We also refer to your submissions dated March 12, April 17, May 12, June 4, and November 11, 2003.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

Chemistry, Manufacturing, and Controls:

1. _____

Labeling and Nomenclature:

2. In the DESCRIPTION section of the package insert, the table of ingredient names and amounts should be clarified as to what amount is considered a "unit dose".
3. In the DOSAGE AND ADMINISTRATION section of the package insert, specify the exact amount of Vial 1 contents to be transferred to Vial 2 (2-vial "kit"). Also, specify which container closure may be penetrated only on time (e.g., Vial 1, Vial 2, or both).
4. In the directions for use of the unit-dose vial, the instructions read "insert vial and withdraw dose in the usual manner". Specify the amount to withdraw from the vial.
5. The aluminum content statement on the immediate containers for Vials 1 and 2 should state _____

6. Provide revised labeling (preferably in electronic format) that incorporates the changes listed above as well as with responses to the comments on the enclosed package insert (PI). (Items 2-4 are also incorporated as comments on the enclosed PI.)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, 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

ENCLOSURE

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-625** Supplement # **N/A**

Trade Name: **M.V.I. Adult**

Generic Name: (multi-vitamins for infusion)

Strengths: single dose (two vials and two-chambered unit vials & pharmacy bulk pack (PBP) (PBP was unbundled and a user fee was paid for a new NDA 21-643- received April 18, 2003)

Applicant: **aai Pharma, Inc.**

Agent: **Astra Zeneca – Matt Arnold**

Date of Application: **28-Feb. 2003**

Date of Receipt: **03-Mar-2003**

Date clock started after UN: **N/A**

Date of Filing Meeting: **22-Apr-2003 (Virtual Mtg)**

Filing Date: **02-May-2003**

74-Day Letter Date: **16-MAY-2003**

Action Goal Date (optional): **10-DEC-2003**

User Fee Goal Date: **03-JAN-2004**

Indication(s) requested: **Daily maintenance multivitamin for patients aged 11 years and older receiving parenteral nutrition or where intravenous administration is required.**

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA _____ **X** _____
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: **S** **X** _____ P _____
Resubmission after a withdrawal? **N/A** _____ Resubmission after a refuse to file? **N/A** _____
Chemical Classification: (1,2,3 etc.) **3** _____
Other (orphan, OTC, etc.) **N/A** _____

User Fee Status: Paid **Y** _____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: **YES**

User Fee ID # **4510**

Clinical data? **YES** _____ **NO**, Referenced to NDA # **FED. REG. NOTICE**

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication?

NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A YES NO

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

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

• Does the submission contain an accurate comprehensive index? YES

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

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

It was submitted without labeling. When labeling was submitted, the immediate container/carton labels did not list ingredients correctly; i.e., vitamin K was omitted. Such labeling was submitted in amendments.

A separate NDA and a separate package insert are required for the PBP. Subsequently NDA 21-643 was submitted for the PBP.

• If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? Labeling

• If in Common Technical Document format, does it follow the guidance? N/A

• Is it an electronic CTD? NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

• Patent information included with authorized signature? YES

• Exclusivity requested? NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure information included with authorized signature? N/A
(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers:
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 27-FEB-2002
NO
If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? N/A
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If parenteral product, consulted to Microbiology Team (HFD-805)? YES

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: This is a reformulation required by Fed. Reg. 65: 21200-1.
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This reformulation adds vitamin K and increases the concentration of four components.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder

was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

X 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

Refers to Fed. Reg. Notice.

YES

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

NO

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

N/A

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?

NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

N/A

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES

NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES

NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

YES, IND # _____

NO

- OR A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A

YES

NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 22, 2003

BACKGROUND: Reformulation of this parenteral adult multivitamin for infusion was required by Federal Register Notices. FDA met with the firm to discuss the possibility of continuing to market its M.V.I.-12 (NDA 8-809) product without Vitamin K and to determine the data requirements for this reformulation on Feb. 7, 2002. Subsequent agreement by the CDER Office of Regulatory Policy and support from the medical officer in DMEDP permitted the continued marketing of NDA 8-809 without vitamin K. However, it was agreed the firm would reformulate that product to increase the concentration of four components mentioned in the FR Notice.

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

ATTENDEES: Comments by email.

ASSIGNED REVIEWERS:

Discipline

Reviewer

Medical:	Jean Temeck (labeling only)
Secondary Medical:	N/A
Statistical:	N/A
Pharmacology:	Dylan Yao (labeling only)
Statistical Pharmacology:	N/A
Chemist:	David Lewis
Environmental Assessment (if needed):	David Lewis
Biopharmaceutical:	N/A
Microbiology, sterility:	V. Pawar
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Manager:	Galliers
Other Consults:	DMETS

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

YES NO

CLINICAL

FILE _____

REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO

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

N/A

CLINICAL MICROBIOLOGY FILE _____ REFUSE TO FILE _____ N/A

STATISTICS FILE _____ REFUSE TO FILE _____ N/A

BIOPHARMACEUTICS FILE _____ REFUSE TO FILE _____ N/A

- Biopharm. inspection needed: YES NO

PHARMACOLOGY FILE _____ REFUSE TO FILE _____ N/A

- GLP inspection needed: YES NO

CHEMISTRY FILE _____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES

- Microbiology YES

ELECTRONIC SUBMISSION: Labeling only.

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

 X No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Document filing issues/no filing issues conveyed to applicant by Day 74.

{See attached electronic signature page.}

Regulatory Project Manager, HFD-510
Enid Galliers, CPMS, DMEDP

C:\Vitamins\21625.Adm-Fil.2.doc
E.Galliers/03.30.2003/05.1.2003/12.04.2003/

**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
12/4/03 07:43:25 PM
CSO

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 18, 2003
NDA NUMBER: 21-625
NAME OF DRUG: M.V.I. Adult (Multi-Vitamins for Infusion)
NDA SPONSOR: AAI Pharma

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products, to review the proprietary name, M.V.I. Adult, regarding potential name confusion with other proprietary and established drug names. The container labels, carton labeling, and package insert were reviewed for safety concerns to minimize medication errors.

In addition, the Division of Metabolic and Endocrine Drug Products (HFD-510) specifically stated that the Division wants to differentiate clearly between the adult products with and without vitamin K.

PRODUCT INFORMATION

AAI Pharma currently markets adult and pediatric commercial parenteral multi-vitamin products. The adult product (M.V.I.-12) contains no vitamin K, whereas the pediatric product (M.V.I. Pediatric) contains vitamin K. Federal Register notice 65 FR 21200 notice indicated approved NDAs for IV multivitamin solutions for adults should be modified (increase dosage of vitamins B1, B6, C, folic acid, and add vitamin K). In lieu of the FR notice, AAI Pharma plans to continue marketing the current formulation without vitamin K but add to the product line a new product that meets all of the FR requirements. The proposed name for the new adult formulation is "M.V.I. Adult". The sponsor feels that the inclusion of either adult or pediatric language in the product's name will designate a complete 13 vitamin formulated product designed for either the adult or pediatric patient. The sponsor will continue to market it's adult parenteral multivitamin without vitamin K under approved NDA 8-809, using the proprietary name "M.V.I. -12".

Thus, AAI Pharma will market three multi-vitamin parenteral products.

Products	Comments
M.V.I.-12 (Multi-Vitamin Infusion)	• Currently marketed product without vitamin K • Indicated for adults and children aged 11 years and above • Proposed modification of the established name from <u>Multi-Vitamin Infusion</u> to
M.V.I. Pediatric (Multi-Vitamins for Infusion)	• Currently marketed product • Indicated for infants and children up to 11 years of age • Contains vitamin K
M.V.I. Adult (Multi-Vitamins for Infusion)	• Proposed proprietary name for new multivitamins for infusions with vitamin K for adults and children aged 11 years and above

M.V.I. Adult is indicated as daily multivitamin maintenance for adults and children aged 11 years and above receiving parenteral nutrition. It is also indicated in other situations where administration by the intravenous route is required. Such situations include surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states, which may provoke a “stress” situation with profound alteration in the body’s metabolic demands and consequent tissue depletion of nutrients. M.V.I. Adult (administered in intravenous fluids under proper dilution) contributes toward the intake of these vitamins that are necessary toward maintaining the body’s normal resistance and repair processes. Patients with multiple vitamin deficiencies or with markedly increased requirements may be given multiples of the daily dosage for two or more days as indicated by the clinical status. M.V.I Adult is an “Aqueous” multivitamin formula for intravenous infusion, which produces a combination of important oil-soluble and water-soluble vitamins in a aqueous solution, formulated for incorporation into intravenous infusions. Through special processing techniques, the liposoluble vitamins A, D, E, and K have been solubilized in an aqueous medium with polysorbate 80, permitting intravenous administration of these vitamins. For intravenous feeding administration, the daily dose of M.V.I. Adult is added directly to not less than 500 mL, preferably 1,000 mL, of intravenous dextrose, saline or similar infusion solutions. M.V.I. Adult is supplied as M.V.I. Adult Dual Vial, M.V.I. Adult Unit Vial, and M.V.I. Adult Multi-dose (pharmacy bulk package). The Dual Vial is comprised of two individual 5 mL vials labeled Vial 1 and Vial 2. The Unit vial is a two-chambered single-dose 10 mL vial that must be mixed just prior to use.

II. RISK ASSESSMENT

The DMETS medication error staff conducted a search of several standard published drug product reference texts¹ as well as several FDA databases² for existing drug names which sound-alike or look-alike to “M.V.I. Adult” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis³ Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, M.V.I. Adult. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have concerns about the name, M.V.I. Adult, with regard to promotional claims.

¹ Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO. <http://www.efactsweb.com/index.asp> MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems and PDR/Physician’s Desk Reference (Medical Economics Company Inc, 2003).

² The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

³ Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at www.thomson-thomson.com

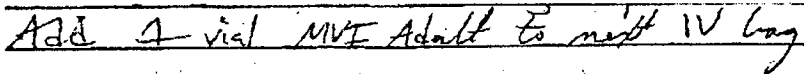
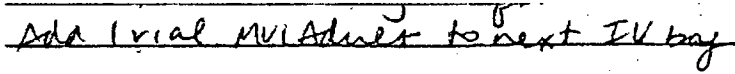
2. The Expert Panel identified M.V.I. Pediatric and M.V.I.-12 as having the potential for confusion with "M.V.I. Adult." These products are listed in Table 1 along with the dosage forms available and usual dosage.

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel			
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
M.V.I. Adult	Injection, Multi-Vitamins for Infusion	For intravenous feeding, one daily dose of M.V.I. Adult (10 mL of Unit vial or 5 mL of Vial 1 plus 5 mL of Vial 2) added directly to not less than 500 mL, preferably 1,000 mL, of intravenous dextrose, saline or similar infusion solutions.	N/A
M.V.I. Pediatric	Injection, Multi-Vitamins for Infusion	According to the child's weight, the doses of M.V.I. PEDIATRIC indicated below are recommended for daily* administration. Each dose should be added to >100 mL dextrose, saline, or similar infusion solution. >3 kg-Add 5 mL; 1-3 kg-Add 3.25 mL; < 1 kg-Add 1.5 mL (do not exceed this dose) * Patients with multiple vitamin deficiencies or with markedly increased requirements may be given multiples of the daily dosage for 2 or more days as indicated by the clinical status. The exception is infants <1 kg, whose daily dosage of M.V.I. PEDIATRIC should never exceed 1.5 mL.	LA/SA
M.V.I.-12	Injection, Multi-Vitamin Infusion	One dose (10 mL final volume) administered daily. Patients with multiple deficiencies or with markedly increased requirements may be given multiples of the daily dosage for 2 or more days as indicated by their clinical	LA/SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

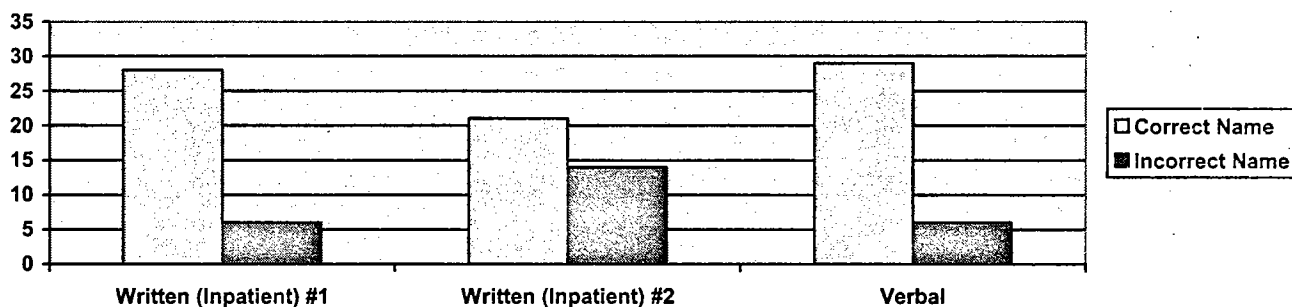
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of M.V.I. Adult with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 129 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote two inpatient prescriptions for M.V.I. Adult, each consisting of a combination of marketed and unapproved drug products. These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Inpatient RX sample 1:</u> 	Add 1 vial MVI Adult to next IV bag.
<u>Inpatient RX sample 2:</u> 	

2. Results for M.V.I. Adult studies

Results of these exercises are summarized below:

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Inpatient #1	43	34 (80%)	28 (82%)	6 (18%)
Written Inpatient #2	43	35 (81%)	21 (60%)	14 (40%)
Verbal	43	35 (81%)	29 (83%)	6 (17%)
Total	129	104 (81%)	78 (75%)	26 (25%)



In the verbal study 6 of 35 (17%) respondents interpreted "M.V.I. Adult" incorrectly. The majority of the incorrect name interpretations were phonetic variations of M.V.I. Adult. These include "...MVI to adult only" (1), "Adult NVI" (1), "Env-I adult" (1), "Imvi" (1), and "M.V.I. (multivitamin, intravenous)" (1). Although, none of the misinterpreted names were similar to an approved product, the misinterpretations included "M.V.I." with the omission of the "Adult" portion of the name.

Among the two written inpatient studies, 20 of 69 (29%) respondents interpreted the name incorrectly. The majority of the misinterpretations included the omission of the "Adult" portion of the name. The most common misinterpretation from the written studies included "M.V.I." and or "multivitamins" (9) and "M.V.I. Adnet"(3). The remaining misinterpretations were "multivitamin Adven" (1), "MVI Adires" (1), "MVI Admet" (1), "MVI Adnes" (1), "MVI Aduet" (1), and "MVI Advet" (1). Although none of the misinterpreted names were similar to an approved product, most of the misinterpretations were "M.V.I." and or "multivitamins" with the omission of the "Adult" portion of the name.

C. ADVERSE EVENT REPORTING SYSTEM (AERS) and DRUG QUALITY REPORTING SYSTEM (DQRS)

A search of the Adverse Event Reporting System (AERS) for medication errors involving MVI% resulted in one relevant case. A search in the Drug Quality Reporting System did not reveal any cases.

ISR # 1994145-3

Unverified report from a pharmacist of a "hear say." An infant received the adult formulation of M.V.I.-12 a couple of weeks ago (approximately mid-September 1997) and experienced a coma for which he/she was treated with UV light. Outcome is unknown.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, M.V.I. Adult, the primary concerns raised were related to two sound and/or look-alike names that currently exist in the market place, MVI Pediatric and MVI-12.

DMETS conducted prescription studies to simulate the prescription ordering process. There was no confirmation that the M.V.I. Adult could be confused with M.V.I. Pediatric or M.V.I. 12. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of interpretations from the verbal and written prescription studies were phonetic or spelling misinterpretations of the drug name, M.V.I. Adult.

1. Potential confusion among M.V.I. products

For patients who should not receive vitamin K, the sponsor plans to continue marketing M.V.I.-12. The two adult formulations (M.V.I.-12 and M.V.I. Adult) have different modifiers but they share the same root name "M.V.I." and additionally, both products will share the same dosing intervals, patient populations, physician populations, route of administration, and packaging configurations.

Potential name confusion between the three products may occur because all three begin with the root name, M.V.I., and have the same dosing interval (once daily IV). Moreover, these products may be stored next to each other in pharmacies which increase the potential for selection errors among the M.V.I. products. DMETS has one post-marketing report of confusion between M.V.I. Pediatric and M.V.I.-12 (predecessor of M.V.I. Adult) where a practitioner dispensed M.V.I.-12 in

lieu of M.V.I. Pediatric. Although, only one report was submitted to the Agency, this postmarketing report indicates that the potential for confusion between products that begin with the same root name (i.e., M.V.I.) exists.

To compound the confusion, parenteral nutrition therapies may be ordered using the established name, "multivitamins", without the modifiers. Hospitals and institutions often order parenteral nutritional therapy according to their formulary requirements and often eliminate the need to order by a specific brand name product. Thus, orders written as "multivitamins" may be misinterpreted as M.V.I.-12 or M.V.I. Adult. Results of the verbal and written Rx studies show a glimpse of potential medication errors which could occur due to omission of modifiers in the product name. For example, in the verbal study, one of the respondents misinterpreted the prescription as "...MVI to adult only". With the availability of two adult products, the order could have easily resulted in selection of M.V.I. -12 rather than M.V.I. Adult or vice versa. The majority of the written study misinterpretations were due to omission of the "Adult" portion of the name. The most common misinterpretation from the written studies was "M.V.I." and or "multivitamins".

There is also a potential for serious clinical consequences if a patient is dispensed M.V.I. Adult instead of M.V.I.-12. Caution should be exercised when administering this multivitamin formulation to patients on warfarin sodium-type anticoagulant therapy. In such patients, vitamin K may antagonize the hypoprothrombinemic response to anticoagulant drugs, therefore requiring dosage adjustment of the warfarin sodium-type anticoagulant therapy.

2. Established Name Confusion

The sponsor proposes to modify the established name of the existing product, M.V.I.-12 from *Multi-vitamin Infusion* to _____ to help distinguish between M.V.I.-12 and M.V.I. Adult formulations. Although, the proposed modified established name will help clarify that M.V.I.-12 is the formulation without vitamin K, the confusion still exists for a potential mix-up between the two adult formulations and or with the pediatric formulation. Perhaps, rather than proposing to change the established name of the older product (M.V.I. -12) to _____, it may be more effective to reinforce the difference in the formulation by addressing the inclusion of vitamin K in the established name of the newer product, M.V.I. Adult (e.g., Multi-Vitamins for Infusion with vitamin K). Due to the long standing use of M.V.I. -12, healthcare practitioners are likely to be already familiar with the formulation and know that M.V.I.-12 does not contain vitamin K.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container labels, carton and insert labeling of M.V.I. Adult, DMETS has attempted to focus on the safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, in effort to minimize potential user error. However, DMETS was unable to conduct a complete review of the labeling due to the illegibility of the labels submitted, especially the bulk containers.

A. GENERAL COMMENTS

DMETS is unable to determine how the colors and design of the final printed labels and labeling will impact the likelihood for errors between M.V.I. -12 and M.V.I. Adult. Currently, the design of M.V.I. Adult and M.V.I.-12 looks identical (container labels and carton labeling). This is especially problematic since the proposed established name for M.V.I. Adult is "Multi-Vitamins for Infusion", which is almost identical to the current established name for M.V.I.-12 (Multi-Vitamin Infusion). This increases the likelihood of product mix-up between M.V.I. Adult and M.V.I.-12. Ensure that there is adequate differentiation in the design of the container and carton labeling for M.V.I. Adult and M.V.I.-12. In addition, to avert potential confusion between the two products, ensure that the M.V.I. Adult vials are readily distinguishable (i.e., color and shape of vials) from M.V.I.-12 vials.

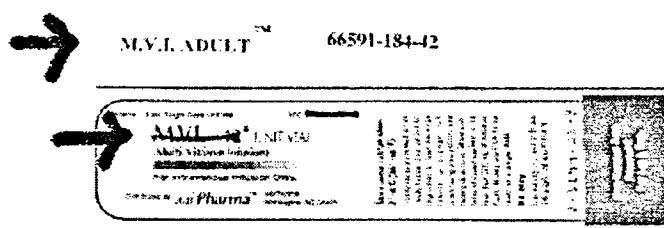


Figure 1. Proposed label and labeling for M.V.I. Adult

B. INSERT LABELING

1. DESCRIPTION

Under Adult formulation is a table of ingredient names and the ingredient amount. Define or clarify what amount is considered "Unit Dose."

2. DOSAGE AND ADMINISTRATION

- Under Directions for Dual Vial, specify the exact amount of contents of Vial 1 to be transferred to Vial 2. Also specify which container closure may be penetrated only one time (ex. Vial 1, Vial 2, or both). The insert also states that the solution should be used immediately after dilution. Specify which solution (ex. Vial 2 or the IV solution).
- Under Direction for Unit-Vial, the sentence reads "Insert vial and withdraw dose in the usual manner." Specify the amount to withdraw from the vial.
- The insert states, "...the resulting solution is ready for immediate use." Define immediate (ex. Within 4 hours etc).

IV. RECOMMENDATIONS

- A. DMETS does not recommend the proprietary name, M.V.I. Adult.
- B. DMETS recommends implementation of the labeling revisions described in Section III.
- C. DDMAC finds the proprietary name, M.V.I. Adult, acceptable from a promotional perspective.
- D. DMETS recommends consulting Dan Boring, Chair of the CDER Labeling and Nomenclature Committee (LNC) on the proposed established name change of the existing M.V.I.-12 product from "Multi-Vitamin Infusion" to "_____".
_____ DMETS recommends the inclusion of vitamin K in the established name of the newer product, M.V.I. Adult (e.g., Multi-Vitamins for Infusion with vitamin K) instead.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Linda Y. Kim-Jung, R.Ph. Date
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

Concur:

Denise Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Linda Kim-Jung
8/15/03 09:40:24 AM
PHARMACIST

Denise Toyer
8/15/03 10:43:34 AM
PHARMACIST

Carol Holquist
8/15/03 10:58:17 AM
PHARMACIST

Jerry Phillips
8/18/03 09:39:14 AM
DIRECTOR



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-625

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 February 27, 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).

We also refer to your submissions dated March 12, April 17, and 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 was filed under section 505(b) of the Act on May 2, 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

5/14/03 08:16:36 PM



NDA 21-625
NDA 21-643

INFORMATION REQUEST LETTER

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

CONSULTATION RESPONSE
Division Of Medication Errors And Technical Support
Office Of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: April 22, 2003	Desired Completion Date: July 20, 2003 PDUFA Date: January 3, 2004	ODS CONSULTS: 03-0152
TO: David Orloff, M.D. Director, Division of Metabolic and Endocrine Drug Products HFD-510		
THROUGH: Enid Galliers Project Manager, Division of Metabolic and Endocrine Drug Products HFD-510		
PRODUCT NAME: M.V.I. Adult (Multi-Vitamins for Infusion) NDA #: 21-625 M.V.I. -12 (Multi-Vitamin Infusion) NDA #: 8-809		NDA SPONSOR: AAI Pharma
SAFETY EVALUATOR: Linda Y. Kim-Jung, R.Ph.		
SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "M.V.I. Adult" to determine the potential for confusion with approved proprietary established names as well as pending names.		
RECOMMENDATIONS: 1. DMETS does not recommend the use of the proprietary name, M.V.I. Adult. 2. DMETS recommends implementation of the labeling revisions described in Section III. 3. DDMAC finds the proprietary name, M.V.I. Adult, acceptable from a promotional perspective. 4. DMETS recommends consulting Dan Boring, Chair of the CDER Labeling and Nomenclature Committee (LNC) on the proposed established name change of the existing M.V.I.-12 product from "Multi-Vitamin Infusion" to "Multi-Vitamin Infusion with Vitamin K". DMETS recommends the inclusion of vitamin K in the established name of the newer product, M.V.I. Adult (e.g., Multi-Vitamins for Infusion with vitamin K) instead.		
Carol Holquist, RPh Deputy Director, Division of Medication Errors and Technical Support Office of Drug Safety Phone: 301-827-3242 Fax: 301-443-9664 Jerry Phillips, RPh Associate Director Office of Drug Safety Center for Drug Evaluation and Research Food and Drug Administration		

REQUEST FOR CONSULTATION

TO (Division/Office):

Director, Division of Medication Errors and Technical Support (DMETS), HFD-420, PKLN Rm. 6-34

FROM:

HFD-510/ Enid Galliers (x 76429)

DATE
19-APRIL-2003

IND NO.

NDA NO.
21-625
8-809

TYPE OF DOCUMENT
N-000 labels & PI
SCF

DATE OF DOCUMENT
27-March-2003

NAME OF DRUG
M.V.I. Adult (multi-vitamins for infusion)
[13 vitamins] (NDA 21-625) &
M.V.I.-12 (multi-vitamins for infusion)
vitamin K) (12 vitamins) (NDA 8-809)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
3

DESIRED COMPLETION DATE
20-JUL-2003

NAME OF FIRM: AAI PHARMA, INC.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

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

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

III. BIOPHARMACEUTICS

- | | |
|--|---|
| ☐ DISSOLUTION | ☐ DEFICIENCY LETTER RESPONSE |
| ☐ BIOAVAILABILITY STUDIES | ☐ PROTOCOL-BIOPHARMACEUTICS |
| ☐ PHASE IV STUDIES | ☐ IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL

☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: A paper copy of labeling plus some comments/proposals from the applicant will be delivered by hand. **The draft PI, two inner labels (Vial 1 and Vial 2), and one outer label for NDA 21-625 are attached and also in EDR.** Note that AAI Pharma will continue to market its adult parenteral multivitamin without vitamin K under approved NDA 8-809. It is required to reformulate this product by adding Vitamin K (and increasing amounts of four current ingredients.) Due to concerns about the possibility that patients taking coumadin might inadvertently receive the product containing vitamin K, the firm and the Division want to differentiate clearly between the adult products with and without vitamin K. The firm proposes to name the reformulated adult product with vitamin K as **M.V.I. Adult** (multi-vitamins for infusion); this name is similar in structure to the Sabex product, Infuvite Adult (multiple vitamins for infusion), which also contains vitamin K. AAI Pharma proposes to call its venerable adult multi-vitamin (without vitamin K) **M.V.I.-12** (AAI Pharma and Sabex market pediatric parenteral multiple vitamins containing

vitamin K under the names M.V.I. Pediatric and Infuvite Pediatric, respectively.)

The draft PI, vial, and carton labels include labeling for three presentations: UNIT VIAL, single dose DUAL VIAL (Vial 1 and Vial 2), a pharmacy bulk package (PBP) "Multi-Dose" (Vial 1 and Vial 2). However, the firm withdrew PBP presentation from this NDA when informed that PBP's are required to have separate NDAs per the User Fee dling policy. The firm will submit a PBP NDA for M.V.I. Adult soon.

NDA 8-809 (Manufacturing supplement and new labeling have not been submitted yet.) THE FOLLOWING INFORMATION WAS SUPPLIED BY AAI PHARMA, INC.

I. Proposed product and established names for our Orphan Drug Product Candidate:

M.V.I.®-12

II. Rationale for proposing this product and established name.

Current commercial M.V.I.® products.

We currently have both an adult and pediatric commercial parenteral multi-vitamin product. The adult product (M.V.I.®-12) contains no vitamin K, whereas our pediatric product (M.V.I.® Pediatric) contains vitamin K. The consumer is familiar with the vitamin status of both of these products based on their long historical use.

Complying with 65 FR 21200.

Based on the directions of this announcement we have executed a plan to produce a comparable adult product to match our pediatric product by adding vitamin K. We propose to name that new product M.V.I. Adult™ to be consistent with M.V.I.® Pediatric. Inclusion of either the adult or pediatric language in the product's name will designate a complete 13 vitamin formulated product designed for either the adult or pediatric patient.

ure commercial products.

Prior to our reformulation project we have not had a product labeled M.V.I. Adult™. Our reformulated product is for use in patients older than 11 years of age and will replace our current M.V.I.®-12 product originally designed for this same population. The result of this reformulation project is that it has created a situation where a small group of patients will be best served if there is also an adult product that does not contain vitamin K.

III. Summary.

Knowing the unique nature of multi-vitamin parenteral products and that the division can determine an established name for these products we request that M.V.I.®-12 be used as the Orphan Drug Candidate product name. In addition, we will clarify its established name to read:

By naming the Orphan Drug Candidate in this way there will be minimal chance of confusion between our two proposed adult multi-vitamin infusion products.

PDUFA DATE: Jan. 3, 2004. DMEDP requests final reviews in DFS by Jul. 20, 2003.

cc: Archival NDA; HFD-510/RPM; HFD-510/Reviewers and Team Leaders

SIGNATURE OF REQUESTER
(See appended electronic signature page.)

METHOD OF DELIVERY (Check one)

☐ MAIL

☐ HAND

URE OF RECEIVER

SIGNATURE OF DELIVERER

**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

4/19/03 11:32:02 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-625

AstraZeneca Pharmaceuticals
Attn: Kevin McKenna
Executive Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. McKenna:

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 Infusion)
Review Priority Classification: Standard (S)
Date of Application: February 27, 2003
Date of Receipt: March 3, 2003
Our Reference Number: NDA 21-625

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 2, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 3, 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:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-625

Page 2

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 & 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

3/10/03 05:32:30 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): HFD-805/ Microbiology Review Staff r. Peter Cooney <i>3/0 Patricia Tuegel</i>		FROM: DMEDP (HFD-510) Enid Galliers/ 14B-19/ x 76429 Mail: 8B-45		
DATE 10-March-2003	IND NO.	NDA NO. 21-625	TYPE OF DOCUMENT NEW NDA	DATE OF DOCUMENT 27-FEB-2003
NAME OF DRUG M.V.I. Adult (multiple vitamins for infusion)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 3	DESIRED COMPLETION DATE A) 4/8/03 Filing Review B) 11/01/03 Application Review
NAME OF FIRM: AAI PHARMA (Agent: ASTRAZENECA)				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☒ FILING MEETING PLANNED BY 4/8/03 ☐ 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 XXX ☐ OTHER (SPECIFY BELOW): New NDA - Micro (sterility) review				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH ☐ TYPE A OR B NDA REVIEW ☒ END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):		STATISTICAL APPLICATION BRANCH ☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES		☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL		☐ PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Dr. V. Pawar participated in the 2/27/02 meeting with the firm to discuss this submission. It is a reformulation of an approved adult multivitamin made in conformance with a Federal Register requirement for reformulation. This product adds vitamin K and increases the amounts of Vit. B1, B6, C, and folic acid. Minutes of that meeting are attached to the MICRO jacket vol. 1.1.				
SIGNATURE OF REQUESTER <i>Enid Galliers</i>		METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

**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

3/10/03 02:15:13 PM

Hard copy (2 volumes) to be delivered by hand.

Please email me with the name of the
micro reviewer.

JUNE 11, 2002

TELECON

5:30 PM

NDA 8-809 & NDA 18-920

Applicant: [REDACTED]

Between: [REDACTED]

And

Enid Galliers, FDA

Mr. [REDACTED] asked for a decision on whether to submit a new NDA or a supplement for the following changes to the approved NDAs.

The firm is required by Fed. Reg. Notice to reformulate its adult multivitamins injections product (NDA 8-809) to add vitamin K and increase folic acid. Previously, the FDA agreed that the firm could continue to market an adult multivitamin product without vitamin K for those patients who should not receive vitamin K. I told Mr. [REDACTED] that the required reformulated product with vitamin K should be submitted as a new NDA.

For the pediatric multivitamins for injection (NDA 18-920, which already contains vitamin K), the firm

[REDACTED]

Enid Galliers
CPMS, DMEDP

**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
6/11/02 06:46:39 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 27, 2002

TIME: 3:30 – 5:00 pm.

LOCATION: Potomac Room 3rd Floor – Parklawn Bldg.

APPLICATION: NDA 8-809 MVI-12 IV Multivitamin → *Applies to NDA 21-625*

TYPE OF MEETING: Pre-Supplement Meeting

MEETING CHAIR: Sheldon Markofsky, Ph.D.
Chemistry Team Leader, HFD-820

MEETING RECORDER: Steve McCort
Regulatory Project Manager, HFD-510

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Sheldon Markofsky, Ph.D.	Chemistry Team Leader	ONDC, DNDC II, HFD-510
2. David Lewis, Ph.D.	Chemistry Reviewer	ONDC, DNDC II, HFD-510
3. Vinnie Pawar, Ph.D.	Microbiology Reviewer	OPS, HFD-805
4. Jean Temeck, M.D.	Medical Reviewer	DMEDP, HFD-510
5. Enid Galliers	Chief Project Management Staff	DMEDP, HFD-510
6.. Steve McCort	Regulatory Project Manager	DMEDP, HFD-510

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Barry Sickels	Director, Regulatory Affairs	Astra Zeneca
2. Diane Alleva	Director, Corporate Technical Services	Astra Zeneca
3. Kathleen Idason	Manager, Operations	Astra Zeneca
4. [REDACTED]	[REDACTED]	[REDACTED]
5. [REDACTED]	[REDACTED]	[REDACTED]
6. Gloria Peters	Associate Director, Biotechnology	AAI International
7. Mathew Arnold	Regulatory Project Associate	Astra Zeneca

BACKGROUND:

In a letter dated February 5, 2002, Astra Zeneca requested a type C meeting to discuss the proposed reformulation plan and timeline for the submission of a supplement for the M.V.I. -12 (Multivitamin Infusion), NDA 8-809.

The firm was responding to the April 20, 2000, Federal Register Notice, The Federal Register notice required all manufacturers of IV Multivitamin adult formulations to reformulate their drug product to include the addition of vitamin K, and increase the amount of vitamins B₁, B₆, C, and folic acid.

On June 15, 2001, Astra Zeneca submitted the response to the Federal Register Notice that included their timeline for submission of a supplement to NDA 8-809 to include CMC information regarding the reformulation. Their proposed date was 1.5 years from the date of the FR notice.

In a telephone call to the firm, dated June 28, 2001, the FDA informed the firm that their proposed date of 1.5 years to submit a supplement to the NDA was acceptable. This would establish the date for the proposed supplemental submission for January 2002.

On February 5, 2002, the firm requested a meeting with FDA. The meeting was granted in a FAX dated February 19, 2002.

MEETING OBJECTIVES:

1. To discuss the following options for reformulation per the April 20th, 2000 Federal Register Notice:
 - a. _____
 - b. _____
 - c. _____
2. To discuss the labeling for the reformulation of the drug product.
3. To discuss the timelines for submission for the reformulated drug product.
4. To discuss the stability and analytical procedures per the questions on page 4 of the February 5, 2002, meeting package.

DISCUSSION POINTS):

1. The Agency has no objections to any of the proposed reformulations regarding chemistry, manufacturing and controls.
2. Regarding the questions proposed from the meeting package, page 4, the Agency had the following responses:

Question 2: Providing that the data are acceptable, is a supplemental NDA containing _____ accelerated (25°C) and long term stability (5°C) data supplemented with _____ data during the review sufficient to grant a _____ expiry for this product?

FDA Response:

No. The tentative expiry will be assigned based on real-time stability data. The submission of _____ stability data upon submission will not allow the accumulation of sufficient stability data within the review clock to assign a _____ expiry. If _____ stability data were available upon submission (amended to _____ during the first review cycle), a review decision could be made between _____ expiry, pending

acceptability of the accelerated stability data, and the acceptability of supporting stability data.

Question 3 Is our approach to the analytical methods acceptable?

FDA Response:

The approach is acceptable, pending satisfactory Method Validation studies covering the new range for those vitamins, for which the concentration has been increased.

Question 4: In order to expedite the manufacture of the pivotal batches, we propose not performing bulk holding time studies on these batches, but rather to perform this determination on batches to be made subsequently. Is this approach acceptable?

FDA Response:

This approach as proposed is acceptable.

Question 1: Is the proposed timeline/submission acceptable to the FDA?

FDA Response:

The sponsor has proposed submitting the supplemental NDA at the beginning of the third quarter, July 2002. If the sponsor plans on submitting minimal stability data at the time of submission and submitting the rest during the review period, the sponsor is liable to qualify for a shortened expiration dating based upon the amount of the stability data upon submitted. For example [redacted] of accelerated and long term stability data upon submission could be amended to [redacted] during the first review cycle (four month goal date); thus, the temporary expiry for the reformulated product would be [redacted]. The proposed submission date of July 2002 for the supplemental NDA would not be adequate to support a [redacted] expiry upon completion of the first review cycle.

Question 5: Is Option 2 an acceptable approach? If so, what type of statements would the Agency expect to appear in the labeling?

FDA Response:

Option 2 with the inclusion of Vitamin K in a separate one-vitamin vial is acceptable to the Agency. The labeling for the product should include, but need not be limited, to the language specified for the package insert in the April 20, 2000 FRN. For example:

Modify the **DOSAGE AND ADMINISTRATION** section to say, "Administer the product in "x" hours" and "Discard after use."

The sponsor currently has data to support stability of the product for 4 hours but they anticipate submission of data to support stability for 24 hours after dilution. The sponsor plans to re-submit the label with some corrections and additions. The Agency may have comments at that time but they are expected to be minor.

In addition to the specific questions, the following issues and concerns were addressed:

1. Option A: Change of _____

FDA Comment:

The sponsor needs to validate the method for determining _____ and for determining the other vitamins contained in the same vial as _____. In addition, a one-time CMC information package should be submitted to the Agency in support of _____ as manufactured by _____. This information may have already been supplied by _____ regarding a previous supplemental application.

Option 2: The use of a separate _____

FDA Comment:

Since the _____ represents a new product, the sponsor will have to submit full stability data on _____ to support the expiration dating period. From a microbiology point of view the sponsor will qualify the _____. However for Options 1A or 1B, the firm may only need requalification of the immediate _____

2. Is the sponsor planning on doing compatibility studies with the TPN mix?

Astra Zeneca's Response:

Yes.

3. If the FDA only allows and approves the new formulation with the addition of Vitamin K to the final products, what would the sponsor have to do to have the original adult parental adult multivitamin formulation remain on the market?

FDA Response:

This discussion was superseded by a post-meeting communication with the Office of Regulatory Policy.

4. Labeling:

FDA Comment:

The firm has chosen to model their new labeling for the reformulated product on Sabex's approved label for the adult product, Infuvite Adult, NDA 21-163. Dr. Temeck had the following additional recommendations to labeling:

- 5. _____ asked what minimal stability data will be needed to submit a supplemental NDA for the new adult formulation.**

FDA Response:

The minimal data that the sponsor will need for the following: _____

POST MEETING NOTE:

On March 7, 2002, the Agency informed the sponsor that their proposal to market the required reformulated product with vitamin K as well as to market a reformulated vitamin K-free product appears to be justified from a clinical perspective.

The Division of Metabolic and Endocrine Drug Products suggests that the firm submit a new NDA for the 13-vitamin product. The application may incorporate by reference all relevant information in NDA 8-809 and should also reference the Federal Register Notice. It will be necessary for the firm to pay the User Fee for an NDA without clinical data.

David Read of Regulatory Policy stated that there should be no problem with accepting the additional formulation. It would not be necessary to amend the FR notice. An approval like this one would fit the category of post-DESI approval.

DECISIONS (AGREEMENTS) REACHED:

The sponsor will reconsider the timeline July 2002 for submitting the supplemental NDA. The timeline may be adjusted based on the information supplied by the Agency at this meeting.

Minutes Preparer: _____

Steve McCort
Regulatory Project Manager, HFD-510

Chair Concurrence: _____

Sheldon Markofsky, Ph.D.
Acting Chemistry Team Leader, HFD-510

ATTACHMENTS/HANDOUTS: Meeting Materials

cc: NDA 8-809

HFD-510Div. Files Files

HFD-SMcCortRPM

HFD-510/Jtemeck/Dlewis/Smarkofsky/Egalliers

HFD-007/DRead

HFD-805/VPowar

Drafted by: SMM/MARCH 11, 2002

Revised by: SMM/March 20, 2002

**Initialed by: J Temeck/3-27-02/3-28-02/Lewis 3-26-02/E Galliers 3-20-02S Markofsky 3-27/02
final:**

MEETING MINUTES

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

/s/

Sheldon Markofsky
4/4/02 08:15:30 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-625	Efficacy Supplement Type SE-	Supplement Number	
Drug: M.V.I. Adult (multivitamins infusion)		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): NDA 18-920 M.V.I. Pediatric, NDA 8-809 M.V.I. 12; NDA 21-643 M.V.I. Adult Pharmacy Bulk Pack	
❖ Application Classifications:			
• Review priority		(X) Standard () Priority	
• Chem class (NDAs only)		3	
• Other (e.g., orphan, OTC)			
❖ User Fee Goal Dates		December 19, 2003	
❖ 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 (X) 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	January 28, 2004
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? <i>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!</i>	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	December 4, 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 () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) 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	December 17, 2003
• Original applicant-proposed labeling	April 17, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS review August 18, 2003; DMEDP internal labeling review December 15, 2003 RPM review January 26, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	December 12, 2003
• Reviews	December 15, 2003; January 26, 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)	Ack letter March 10, 2003; FN letter May 14, 2003; IR letter May 14, 2003; DR letter December 11, 2003; AE letter December 18, 2003
❖ Memoranda and Telecons	April 1, 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: Filing Meeting	April 22, 2003
❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	FRN April 20, 2000
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	July 24, 2003
❖ Microbiology (efficacy) review(s) (indicate date for each review)	August 27, 2003
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	January 28, 2004
❖ Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	
❖ Biopharmaceutical review(s) (indicate date for each review)	
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	December 12 and 22, 2003; April 1, 2003
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	August 27, 2003
❖ Facilities inspection (provide EER report)	Date completed: December 18, 2003 (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)	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

Blank Page

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
nulldate