

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-625

CHEMISTRY REVIEW(S)



NDA 21-625

M.V.I. Adult (Multi-Vitamin Infusion)

aaPharma

David B. Lewis, Ph.D.

HFD-510 (DMEDP)

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Chemistry Review Data Sheet

1. NDA 21-625
2. REVIEW #: 2
3. REVIEW DATE: December 19th, 2003
4. REVIEWER: David B. Lewis, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 8-809 ORIGINAL NDA	APPROVED IN 1953
NDA 18-920 GENERAL CORRESPONDENCE	18/08/00
DEFICIENCY LETTER	11/12/03
NDA 21-625 CMC REVIEW # 1	12/12/03

- NDA 21-625 CMC Review # 1 was signed off on December 12th, 2003 with the recommendation of APPROVABLE (AE).
- A deficiency letter regarding the drug product labeling was communicated to the NDA sponsor on December 11th, 2003.

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
ORIGINAL (CMC Review # 1)	27/02/03
AMENDMENT (CMC Review # 1)	17/04/03
AMENDMENT (CMC Review # 1)	12/05/03
AMENDMENT (CMC Review # 1)	04/06/03
AMENDMENT (CMC Review # 1)	11/11/03
AMENDMENT (CMC Review # 2)	12/12/03

Chemistry Review Data Sheet

- The amendment dated April 17th, 2003 provides a listing of manufacturing and testing locations for the drug product, a listing of manufacturers for the drug substances, and approved and proposed (new) product specifications.
- The amendment dated May 12th, 2003 provides updated stability data for the drug product, analytical methodology (and validation) for the determination of Vitamin K₁ in the drug product, and a catalogue of the primary packaging components for the drug product.
- The amendment dated June 4th, 2003 provides a commitment to revise the specification for *dl*- α -tocopheryl acetate (Vitamin E, USP) to include a test for benzo(a)pyrene and an acceptance criterion of "NMT 1 ppb". This revision will be submitted to the Agency via CBE supplement within 6 months of approval of NDA 21-625.
- The amendment dated November 11th, 2003 provides responses to information requests regarding analytical methods, testing facilities, container/closure sizes, and instructions for use.
- The amendment dated December 12th, 2003 provides revised labeling in response to a labeling deficiency letter communicated to the NDA holder on December 11th, 2003.

7. NAME & ADDRESS OF APPLICANT:

Name: aaiPharma
Address: 2320 Scientific Park Drive, Wilmington, NC
28405
AstraZeneca Pharmaceuticals LP
Representative: 1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355
Matthew E. Arnold (Regulatory Project Manager)
Telephone: (302) 886-3303 (Phone)
(302) 886-2822 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: M.V.I.TM Adult
- b) Non-Proprietary Name (USAN): Multi-Vitamin Infusion
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)



10. PHARMACOL. CATEGORY: Small Volume Parenteral (SVP)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: The drug product contains the following amounts of drug substances (per 5 mL):

- Ascorbic acid, USP (Vitamin C): 200 mg
- Retinol (Vitamin A, USP): 1 mg
- Ergocalciferol, USP (Vitamin D₂): 5 µg
- Riboflavin 5'-phosphate sodium, USP (Vitamin B₂): 3.6 mg
- Pyridoxine•HCl, USP (Vitamin B₆): 6 mg
- Niacinamide, USP: 40 mg
- Dexpantenol, USP: 15 mg
- *dl*-α-Tocopheryl acetate (Vitamin E, USP): 10 mg
- Thiamine•HCl, USP (Vitamin B₁): 6 mg
- _____
- Biotin, USP: 60 mcg
- Folic acid, USP: 600 mcg
- Cyanocobalamin, USP (Vitamin B₁₂): 5 mcg

Comments: The formula amounts of retinol, ergocalciferol, riboflavin, niacinamide, dexpantenol, vitamin E, biotin, and cyanocobalamin are unchanged from the previously approved formula amounts from NDA 8-809 (M.V.I.-12®). The formula amounts of pyridoxine, thiamine, ascorbic acid, and folic acid for this NDA represents an increase from the previously approved quantities under NDA 8-809 (65 FR 21200). _____ was not included in the formula for NDA 8-809, but was added to the formula for this NDA (65 FR 21200).

13. ROUTE OF ADMINISTRATION: Intravenous (IV)

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

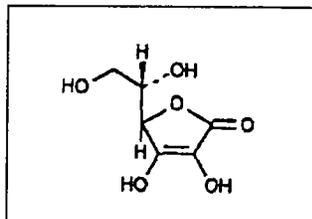
SPOTS product – Form Completed

Not a SPOTS product

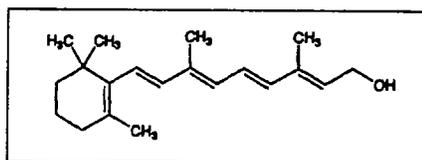
Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

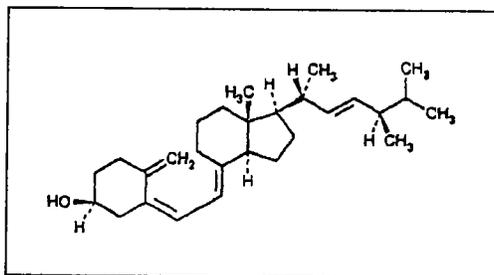
- Ascorbic acid, USP
C₆H₈O₆ (176.12 g/mol)
(Vitamin C)



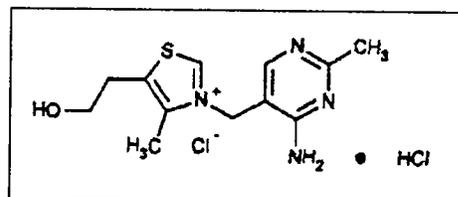
- Retinol
C₂₀H₃₀O, 286.4 g/mol
(Vitamin A, USP)



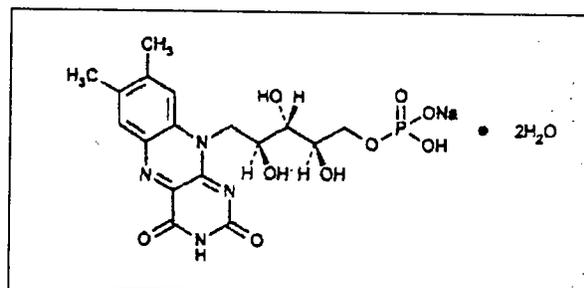
- Ergocalciferol, USP
C₂₇H₄₄O, 396.65 g/mol
(Vitamin D₂), C₂₇H₄₄O



- Thiamine Hydrochloride, USP
C₁₂H₁₇ClN₄OS • HCl, 337.27 g/mol
(Vitamin B₁)

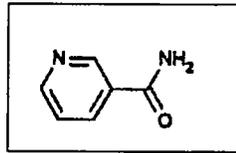


- Riboflavin 5'-Phosphate Sodium, USP
C₁₇H₂₀N₄NaO₉P • 2H₂O, 514.36 g/mol
(Vitamin B₂)

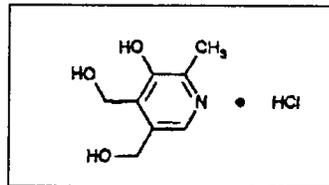


Chemistry Review Data Sheet

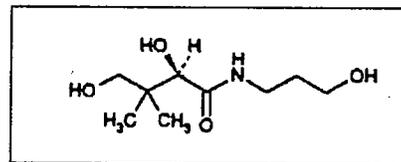
- Niacinamide, USP
 $C_6H_6N_2O$, 122.12 g/mol



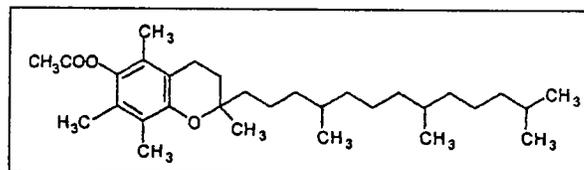
- Pyridoxine Hydrochloride, USP
 $C_8H_{11}NO_3 \cdot HCl$, 205.64 g/mol
(Vitamin B₆)



- Dexpanthenol, USP
 $C_9H_{19}NO_4$, 205.25 g/mol
(Vitamin B₅)

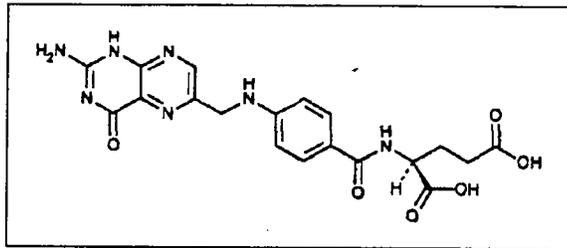


- *dl*- α -tocopherol acetate
 $C_{31}H_{52}O_3$, 472.76 g/mol
(Vitamin E, USP)

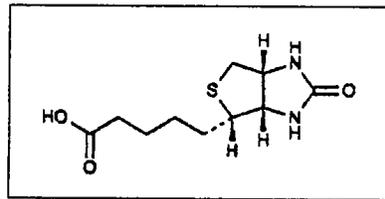


Chemistry Review Data Sheet

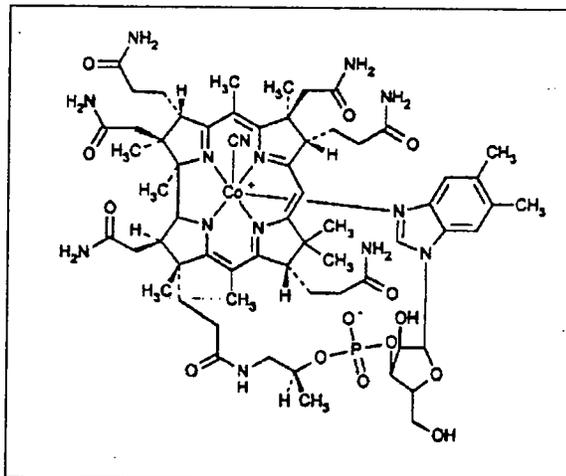
- Folic acid, USP
 $C_{19}H_{19}N_7O_6$, 441.40 g/mol



- Biotin, USP
 $C_{10}H_{16}N_2O_3S$, 244.31 g/mol



- Cyanocobalamin, USP
 $C_{63}H_{88}CoN_{14}O_{14}P$, 1355.37 g/mol
(Vitamin B₁₂)



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	18/12/97	
				3	Adequate	31/12/01	
				3	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Federal Register Notice of April 20 th , 2000	65 FR 21200	Requirement for re-formulation of adult multivitamin injection drug products.
General Correspondence dated August 18 th , 2000	18-920	CMC information regarding bulk vitamin substances manufactured and supplied by _____



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	18/12/03	S. Adams
Pharm/Tox	N/A		
LNC	ACCEPTABLE*	09/12/03	D. Boring (verbal consult)
Methods Validation	Post-approval		
ODS	NOT ACCEPTABLE**	15/08/03	L. Kim-Jung
EA	Categorical exclusion	This review	D. Lewis
Microbiology	ACCEPTABLE	27/08/03	P. Stinavage

* The proposed proprietary and established names for the drug product were discussed and found acceptable in a conversation between D. Lewis (CMC reviewer) and D. Boring (Chairman of LNC and FDA expert in Nomenclature and Labeling).

** The Division of Metabolic and Endocrine Drug Products (DMEDP, HFD-510) has decided to accept the proposed proprietary and established names for the drug product, even though the ODS consult review recommended non-acceptance of these names. ONDC and LNC concur with the opinion of the DMEDP division director.

The Chemistry Review for NDA 21-625

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend APPROVAL from the standpoint of Chemistry, Manufacturing and Controls.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

This NDA (21-625) provides chemistry, manufacturing and controls (CMC) information on the drug product, M.V.I. Adult™ (Multi-Vitamin Infusion). The NDA product represents a reformulation of the approved NDA 8-809, which was originally named M.V.I.-12® (Multi-Vitamins for Infusion). This NDA was filed per the Federal Register Notice dated April 20th, 2000 (65 FR 21200), which mandated the addition of vitamin K and revisions to the formula amounts of vitamins B₁, B₆, C, and folic acid. Normally, the reformulation would be submitted via a prior-approval supplemental NDA, but, in this case, the NDA sponsor (aaiPharma) received FDA approval to concurrently market a 13-vitamin adult multi-vitamin injection (this NDA, including vitamin K) and a 12-vitamin adult multi-vitamin injection (under NDA 8-809, with the reformulated amounts of vitamins B₁, B₆, C, and folic acid per 65 FR 21200, but without vitamin K). Submission of the proposed reformulation of the 12-vitamin drug product is pending. This agreement between aaiPharma and the Agency was reached in a meeting held on February 27th, 2002. In another meeting (March 7th, 2003), the Agency agreed to allow aaiPharma to incorporate relevant CMC information for this NDA by reference to the approved NDA 8-809.

All CMC issues regarding manufacturing process, drug substance testing, drug product testing, container/closure, and stability were found adequate in CMC Review # 1, dated December 12th, 2003. CMC Review # 2 (this review) addresses the resolution of the deficiencies from CMC Review # 1: *GMP status of the application* (specifically, the AstraZeneca manufacturing and testing facility in Westborough, MA) and *drug product labeling*. The Office of Compliance (OC) has found the manufacturing and testing facilities for this NDA acceptable (EER Summary report dated December 18th, 2003).

Executive Summary Section

A. Description of the Drug Product(s) and Drug Substance(s)

The NDA 21-625 drug product is named M.V.I. Adult® (Multi-Vitamin Infusion); the previous (prior to reformulation) drug product filed under NDA 8-809 was named M.V.I.-12® (Multi-Vitamin Infusion), and contained 12 vitamin substances. *The reformulated product filed under NDA 21-625 contains 13 vitamin substances, making the previous drug product name unsuitable.* The proposed established name "Multi-Vitamin Infusion" is the same as the established name for the previously approved 12-vitamin product, M.V.I.-12® (NDA 8-809), which will be marketed concurrently with M.V.I. Adult®. This established name was evaluated and found to be unacceptable by the Office of Drug Safety (ODS). The sponsor proposed changing the established name of M.V.I.-12, to _____ ONDC (this reviewer) and the DMEDP Division Director have accepted this proposal: *The established name for NDA 21-625 should be "Multi-Vitamin Infusion", and proposed proprietary name "M.V.I. Adult®" is acceptable, and the established name for the related product, M.V.I.-12® (NDA 8-809) should be changed to _____*

The labeling for the drug product was reviewed in CMC # 1, and found to be deficient. A deficiency letter was communicated to the NDA sponsor on December 11th, 2003. The NDA sponsor submitted revised labeling via secure E-Mail on December 12th, 2003, which was acceptable (corresponded with the FDA requests).

M.V.I.-Adult™ contains 13 vitamin substances divided into two separate solutions. Solution 1 contains ascorbic acid (Vitamin C, 200 mg/5mL), retinol (Vitamin A, 1 mg/5mL), *dl*- α -tocopheryl acetate (Vitamin E, 10 mg/5mL), ergocalciferol (Vitamin D₂, 5 mcg/5mL), thiamine hydrochloride (Vitamin B₁, 6 mg/5mL), _____, pyridoxine hydrochloride (Vitamin B₆, 6 mg/5mL), niacinamide (40 mg/5mL), riboflavin (Vitamin B₂, 3.6 mg/5mL), and dexpanthenol (15 mg/5mL). Solution 2 contains biotin (60 mcg/5mL), cyanocobalamin (Vitamin B₁₂, 5 mcg/5mL), and folic acid (600 mcg/5mL). The composition for solutions 1 and 2 was defined (mandated) in 65 FR 21200. The drug product is supplied as a sterile solution for IV infusion. There are two package presentations covered by NDA 21-625: a single-dose "kit" containing two separate vials, and a dual-chamber unit-dose vial, in which the vial 1 and 2 solutions described above are separated by an _____ plug situated between the two chambers. NDA 21-625 includes reference to a "multi-dose" drug product. This "multi-dose" product is actually a pharmacy bulk packaged (PBP) injection, and was subsequently submitted via NDA 21-643 per the ONDC/CDER bundling policy which requires PBP drug products to be filed under separate NDA's from their non-PBP related drug products. CMC information regarding the PBP "multi-dose" drug product is not addressed in this review.

All of the drug substances in M.V.I.-Adult™ comply with current USP compendial monographs and are also controlled for endotoxins and bioburden. None of these materials are covered by a currently maintained drug master file (DMF), and are not manufactured under cGMP conditions. CMC information regarding the drug substances is provided by the original NDA 8-809. CMC information for Vitamin K was referred to the related NDA

Executive Summary Section

18-920 (M.V.I. Pediatric), since the NDA 8-809 drug product did not contain Vitamin K. The manufacturers and/or suppliers of the bulk vitamin substances have not been changed as a result of this NDA.

The Office of Compliance (OC) issued a recommendation of **acceptable** for NDA 21-625 (EER Summary Report dated December 18th, 2003). **Note:** The drug substance manufacturing facilities were not inspected, since bulk vitamin drug substances are considered to be foods (nutritionals), and are not manufactured under drug cGMP's.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended for use as a single-dose vial (*prepared by the combination of the vial 1 and 2 contents*). There are two package presentations provided in NDA 21-625; a *single-dose 2-vial "kit"*, consisting of two separate 10-mL glass vials sealed with _____ stoppers and a *unit-dose product packaged in a dual-chambered vial*, in which the two vitamin solutions are separated by an _____ plug. *M.V.I. Adult™* is labeled as a *total parenteral nutritional (TPN) additive*, to be added to a TPN admixture for nutritional support in NPO (*nil per os*, or "nothing by mouth") patients. The usual labeled dose is one vial daily in patients greater than 11 years of age (there is a corresponding pediatric drug product, NDA 18-920, which covers the patient population < 11 years of age).

M.V.I.-Adult™ is neither a pharmacy bulk package nor a multi-dose container. The vial 1 and 2 solutions are mixed prior to addition to TPN admixtures by aseptically transferring the contents of vial 1 into vial 2 and mixing. The unit-dose product solutions are mixed prior to addition to a TPN admixture by forcing the plunger-stopper (which separates the two chambers) into the lower chamber (along with the contents of the upper chamber).

The expiration dating period for M.V.I.® Adult is 18 months for the single-dose vials and 15 months for the unit-dose (dual-chambered) vials with refrigerated storage (2-8°C). This expiry is supported by full-time stability data on the previously approved 12-vitamin product, M.V.I.-12® (NDA 8-809), full-time stability data on the presently approved 13-vitamin pediatric product, M.V.I. Pediatric® (NDA 18-920), and _____ of accelerated (25°C) stability data and associated long-term stability data on three lots each of the single-dose (2-vial kit) and unit-dose (dual chambered vial) presentations of the proposed reformulated M.V.I.® Adult. A larger-than expected loss of vitamin E potency was observed during stability testing of the unit-dose package presentation (approximately _____ loss of initial potency within _____ of storage at 2-8°C). However, the potency assay values were within specified limits after _____, which is only _____ less than the proposed expiration dating period (15 months). On the basis of risk-based review, the vitamin E stability data was found to be acceptable.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for approval (AP):

- CMC information for the drug substances is adequate (identical to that approved for NDA's 8-809 and 18-920).
- The drug product manufacturing processes are essentially identical to those approved for NDA's 8-809 and 18-920, and were found adequate for this NDA.
- The components and composition correspond to those listed in the FR notice of April 20th, 2000, and are essentially the same as those for NDA 18-920 (M.V.I. Pediatric).
- The container/closure system is unchanged from that approved for NDA's 8-809 and 18-920, and was found adequate for this NDA.
- The stability data set supports the proposed expiration dating period (15 months for the unit-dose containers and 18 months for the single-dose "kits", which were approved for NDA 8-809).
- The labeling for the drug product was revised (amendment dated December 12th, 2003) per FDA recommendations, and is now acceptable for this drug product.
- The cGMP status for all manufacturing and testing sites is satisfactory per OC recommendation (EER Summary report dated December 18th, 2003).

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

David Lewis/December 22nd, 2003
Mamta Gautam-Basak/Date
Holly Wieland/Date

C. CC Block



16 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

/s/

David Lewis

12/22/03 02:50:46 PM

CHEMIST

The application may be approved from the standpoint of CMC.
Corrected Index. Revised approval statement (Ex. Summ.). See statement
regarding non-GMP status of vitamin-manufacturing facilities (p. 15).
Cross-referenced all amendments.

Mamta Gautam-Basak

12/22/03 02:59:09 PM

CHEMIST

Concur



NDA 21-625

M.V.I. Adult (Multi-vitamin Infusion)

aaPharma

David B. Lewis, Ph.D.

HFD-510 (DMEDP)

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Chemistry Review Data Sheet

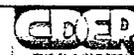
1. NDA 21-625
2. REVIEW #: 1
3. REVIEW DATE: December 12th, 2003
4. REVIEWER: David B. Lewis, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 8-809 ORIGINAL NDA	APPROVED IN 1953
NDA 18-920 GENERAL CORRESPONDENCE	18/08/00
s-NDA 8-809/SCP-024	27/03/90
s-NDA 8-809/SCP-027	19/05/92
s-NDA 8-809/SCP-038	12/11/97

- The general correspondence filed to NDA 18-920 on August 18th, 2000 provided chemistry, manufacturing and controls (CMC) information for the nine (9) bulk vitamins manufactured and supplied from [REDACTED] to AstraZeneca for use in the manufacture of M.V.I.-12® (NDA 8-809) and M.V.I. Pediatric (18-920). This submission was filed to NDA 18-920 only, but pertains to both NDA's. AstraZeneca was the NDA applicant at the time of the CMC submission; aaiPharma is now the NDA applicant for both of the M.V.I. products.
- The supplemental application sNDA 8-809/S-024 provided for the use of the [REDACTED] stopper for the single-use vials (approved on December 7th, 1990). This stopper, though approved, was not used for about 12 years. The alternate stopper [REDACTED] was utilized exclusively for the drug product. The NDA applicant (aaiPharma) reverted back to the [REDACTED] stopper for M.V.I. Adult products about 18 months ago.
- sNDA 8-809/S-027 provided for the use of the [REDACTED] stopper.
- sNDA 8-809/S-038 provided for the use of the reformulated [REDACTED] stopper, replacing the [REDACTED] closure.



CHEMISTRY REVIEW



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6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
ORIGINAL	27/02/03
AMENDMENT	17/04/03
AMENDMENT	12/05/03
AMENDMENT	04/06/03
AMENDMENT	11/11/03

- The amendment dated April 17th, 2003 provides a listing of manufacturing and testing locations for the drug product, a listing of manufacturers for the drug substances, and approved and proposed (new) product specifications.
- The amendment dated May 12th, 2003 provides updated stability data for the drug product, analytical methodology (and validation) for the determination of Vitamin K₁ in the drug product, and a catalogue of the primary packaging components for the drug product.
- The amendment dated June 4th, 2003 provides a commitment to revise the specification for *dl*- α -tocopheryl acetate (Vitamin E, USP) to include a test for benzo(a)pyrene and an acceptance criterion of "NMT 1 ppb". This revision will be submitted to the Agency via CBE supplement within 6 months of approval of NDA 21-625.
- The amendment dated November 11th, 2003 provides responses to information requests regarding analytical methods, testing facilities, container/closure sizes, and instructions for use.

7. NAME & ADDRESS OF APPLICANT:

Name: aaiPharma
Address: 2320 Scientific Park Drive, Wilmington, NC
28405
AstraZeneca Pharmaceuticals LP
Representative: 1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355
Matthew E. Arnold (Regulatory Project Manager)
Telephone: (302) 886-3303 (Phone)
(302) 886-2822 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: M.V.I.TM Adult
- b) Non-Proprietary Name (USAN): Multi-vitamin infusion
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):



CHEMISTRY REVIEW



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- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Small Volume Parenteral (SVP)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: The drug product contains the following amounts of drug substances (per 5 mL):

- Ascorbic acid, USP (Vitamin C): 200 mg
- Retinol (Vitamin A, USP): 1 mg
- Ergocalciferol, USP (Vitamin D₂): 5 µg
- Riboflavin 5'-phosphate sodium, USP (Vitamin B₂): 3.6 mg
- Pyridoxine•HCl, USP (Vitamin B₆): 6 mg
- Niacinamide, USP: 40 mg
- Dexpanthenol, USP: 15 mg
- *dl*- α -Tocopheryl acetate (Vitamin E, USP): 10 mg
- Thiamine•HCl, USP (Vitamin B₁): 6 mg
- ~~_____~~
- Biotin, USP: 60 mcg
- Folic acid, USP: 600 mcg
- Cyanocobalamin, USP (Vitamin B₁₂): 5 mcg

Comments: The formula amounts of retinol, ergocalciferol, riboflavin, niacinamide, dexpanthenol, vitamin E, biotin, and cyanocobalamin are unchanged from the previously approved formula amounts from NDA 8-809 (M.V.I.-12®). The formula amounts of pyridoxine, thiamine, ascorbic acid, and folic acid for this NDA represents an increase from the previously approved quantities under NDA 8-809 (65 FR 21200). ~~_____~~ was not included in the formula for NDA 8-809, but was added to the formula for this NDA (65 FR 21200).

13. ROUTE OF ADMINISTRATION: Intravenous (IV)

14. Rx/OTC DISPENSED: Rx OTC

Chemistry Review Data Sheet

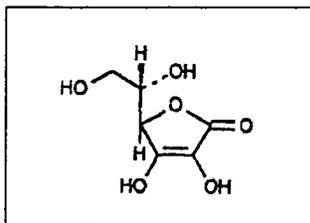
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

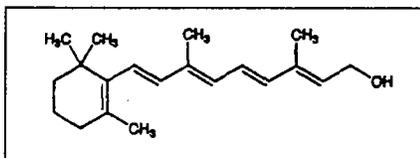
X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

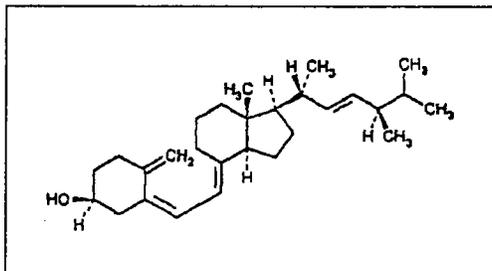
- Ascorbic acid, USP
C₆H₈O₆ (176.12 g/mol)
(Vitamin C)



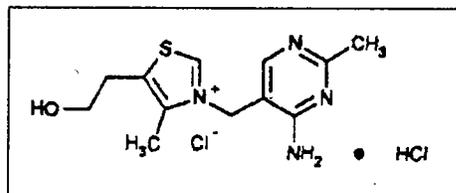
- Retinol
C₂₀H₃₀O, 286.4 g/mol
(Vitamin A, USP)



- Ergocalciferol, USP
C₂₇H₄₄O, 396.65 g/mol
(Vitamin D₂), C₂₇H₄₄O

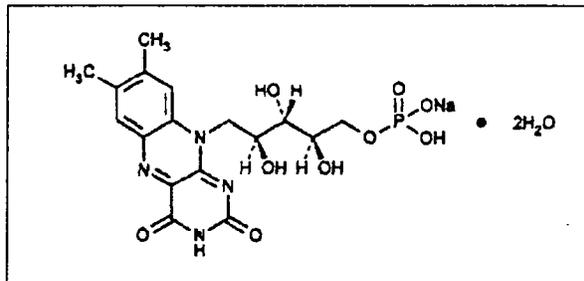


- Thiamine Hydrochloride, USP
C₁₂H₁₇ClN₄OS • HCl, 337.27 g/mol
(Vitamin B₁)

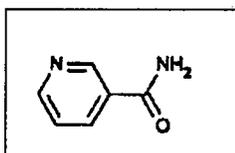


Chemistry Review Data Sheet

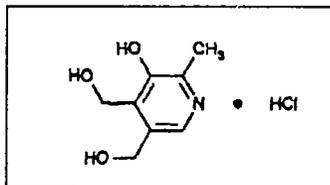
- Riboflavin 5'-Phosphate Sodium, USP
 $C_{17}H_{20}N_4NaO_9P \cdot 2H_2O$, 514.36 g/mol
 (Vitamin B₂)



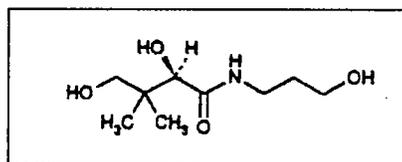
- Niacinamide, USP
 $C_6H_6N_2O$, 122.12 g/mol



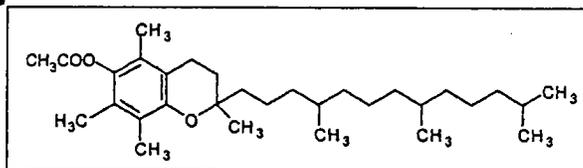
- Pyridoxine Hydrochloride, USP
 $C_8H_{11}NO_3 \cdot HCl$, 205.64 g/mol
 (Vitamin B₆)



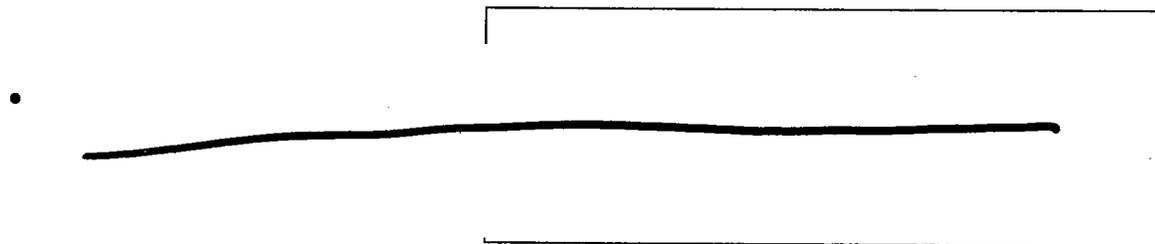
- Dexpantenol, USP
 $C_9H_{19}NO_4$, 205.25 g/mol
 (Vitamin B₅)



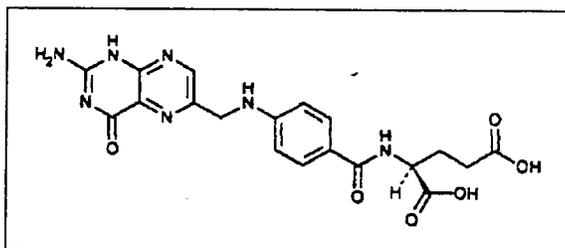
- *dl*- α -tocopherol acetate
 $C_{31}H_{52}O_3$, 472.76 g/mol
 (Vitamin E, USP)



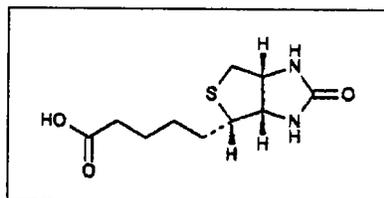
Chemistry Review Data Sheet



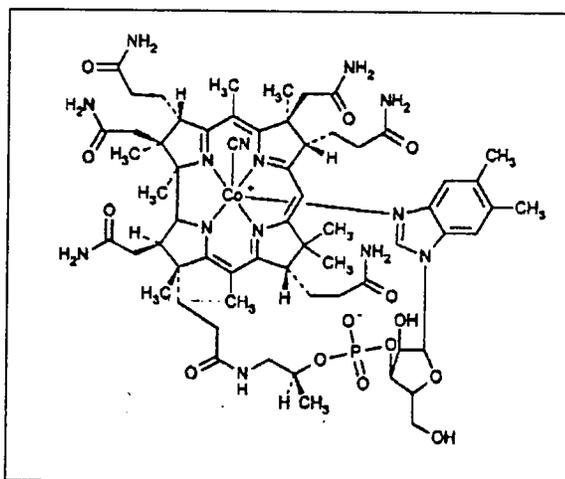
- Folic acid, USP
 $C_{19}H_{19}N_7O_6$, 441.40 g/mol



- Biotin, USP
 $C_{10}H_{16}N_2O_3S$, 244.31 g/mol



- Cyanocobalamin, USP
 $C_{63}H_{88}CoN_{14}O_{14}P$, 1355.37 g/mol
(Vitamin B₁₂)





CHEMISTRY REVIEW



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	18/12/97	
				3	Adequate	31/12/01	
				3	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Federal Register Notice of April 20 th , 2000	65 FR 21200	Requirement for re-formulation of adult multivitamin injection drug products.
General Correspondence dated August 18 th , 2000	18-920	CMC information regarding bulk vitamin substances manufactured and supplied by _____



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18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	WITHHOLD	17/09/03	J. D'Ambrogio
Pharm/Tox	N/A		
LNC	ACCEPTABLE*	09/12/03	D. Boring (verbal consult)
Methods Validation	Post-approval		
ODS	NOT ACCEPTABLE**	15/08/03	L. Kim-Jung
EA	Categorical exclusion	This review	D. Lewis
Microbiology	ACCEPTABLE	27/08/03	P. Stinavage

* The proposed proprietary and established names for the drug product were discussed and found acceptable in a conversation between D. Lewis (CMC reviewer) and D. Boring (Chairman of LNC and FDA expert in Nomenclature and Labeling).

** The Division of Metabolic and Endocrine Drug Products (DMEDP, HFD-510) has decided to accept the proposed proprietary and established names for the drug product, even though the ODS consult review recommended non-acceptance of these names. ONDC and LNC concur with the opinion of the DMEDP division director.

The Chemistry Review for NDA 21-625

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable pending a satisfactory cGMP profile from the Office of Compliance and satisfactory responses to the CMC information requests (labeling) attached to the end of this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

This NDA (21-625) provides chemistry, manufacturing and controls (CMC) information on the drug product, M.V.I. Adult™ (Multi-vitamin infusion). The NDA product represents a reformulation of the approved NDA 8-809, which was originally named M.V.I.-12® (Multi-Vitamins for Infusion). This NDA was filed per the Federal Register Notice dated April 20th, 2000 (65 FR 21200), which mandated the addition of vitamin K and revisions to the formula amounts of vitamins B₁, B₆, C, and folic acid. Normally, the reformulation would be submitted via a prior-approval supplemental NDA, but, in this case, the NDA sponsor (aaiPharma) received FDA approval to concurrently market a 13-vitamin adult multi-vitamin injection (this NDA, including vitamin K) and a 12-vitamin adult multi-vitamin injection (under NDA 8-809, with the reformulated amounts of vitamins B₁, B₆, C, and folic acid per 65 FR 21200, but without vitamin K). Submission of the proposed reformulation of the 12-vitamin drug product is pending. This agreement between aaiPharma and the Agency was reached in a meeting held on February 27th, 2002. In another meeting (March 7th, 2003), the Agency agreed to allow aaiPharma to incorporate relevant CMC information for this NDA by reference to the approved NDA 8-809.

A. Description of the Drug Product(s) and Drug Substance(s)

The NDA 21-625 drug product is named M.V.I. Adult® (Multi-vitamin infusion); the previous (prior to reformulation) drug product filed under NDA 8-809 was named M.V.I.-12® (Multi-vitamin infusion), and contained 12 vitamin substances. *The reformulated product filed under NDA 21-625 contains 13 vitamin substances, making the previous drug product name unsuitable.* The proposed established name "Multi-vitamin infusion" is the same as the established name for the previously approved 12-vitamin product, M.V.I.-12® (NDA 8-809), which will be marketed concurrently with M.V.I. Adult®. This established

Executive Summary Section

name was evaluated and found to be unacceptable by the Office of Drug Safety (ODS). The sponsor proposed changing the established name of M.V.I.-12, to " ". ONDC (this reviewer) and the DMEDP Division Director have accepted this proposal: *The established name for NDA 21-625 should be "Multi-vitamin infusion", and proposed proprietary name "M.V.I. Adult®" is acceptable, and the established name for the related product, M.V.I.-12® (NDA 8-809) should be changed to*

M.V.I.-Adult™ contains 13 vitamin substances divided into two separate solutions. Solution 1 contains ascorbic acid (Vitamin C, 200 mg/5mL), retinol (Vitamin A, 1 mg/5mL), *dl*- α -tocopheryl acetate (Vitamin E, 10 mg/5mL), ergocalciferol (Vitamin D₂, 5 mcg/5mL), thiamine hydrochloride (Vitamin B₁, 6 mg/5mL), , pyridoxine hydrochloride (Vitamin B₆, 6 mg/5mL), niacinamide (40 mg/5mL), riboflavin (Vitamin B₂, 3.6 mg/5mL), and dexpanthenol (15 mg/5mL). Solution 2 contains biotin (60 mcg/5mL), cyanocobalamin (Vitamin B₁₂, 5 mcg/5mL), and folic acid (600 mcg/5mL). The composition for solutions 1 and 2 was defined (mandated) in 65 FR 21200. The drug product is supplied as a sterile solution for IV infusion. There are two package presentations covered by NDA 21-625: a single-dose "kit" containing two separate vials, and a dual-chamber unit-dose vial, in which the vial 1 and 2 solutions described above are separated by an plug situated between the two chambers. NDA 21-625 includes reference to a "multi-dose" drug product. This "multi-dose" product is actually a pharmacy bulk packaged (PBP) injection, and was subsequently submitted *via* NDA 21-643 per the ONDC/CDER bundling policy which requires PBP drug products to be filed under separate NDA's from their non-PBP related drug products. CMC information regarding the PBP "multi-dose" drug product is not addressed in this review.

All of the drug substances in M.V.I.-Adult™ comply with current USP compendial monographs and are also controlled for endotoxins and bioburden. None of these materials are covered by a currently maintained drug master file (DMF), and are not manufactured under cGMP conditions. CMC information regarding the drug substances is provided by the original NDA 8-809. CMC information for Vitamin K was referred to the related NDA 18-920 (M.V.I. Pediatric), since the NDA 8-809 drug product did not contain Vitamin K. The manufacturers and/or suppliers of the bulk vitamin substances have not been changed as a result of this NDA.

The Office of Compliance (OC) recommended *withholding approval (WD)* for the manufacturing facility for the drug product (AstraZeneca, Westborough, Massachusetts). All other facilities involved in the manufacture, filling, and testing of the drug product were found acceptable by the OC.

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

The drug product is intended for use as a single-dose vial (*prepared by the combination of the vial 1 and 2 contents*). There are two package presentations provided in NDA 21-625; a *single-dose 2-vial "kit"*, consisting of two separate 10-mL glass vials sealed with _____ stoppers and a *unit-dose product packaged in a dual-chambered vial*, in which the two vitamin solutions are separated by _____ plug. *M.V.I. Adult™* is labeled as a *total parenteral nutritional (TPN) additive*, to be added to a TPN admixture for nutritional support in NPO (*nil per os*, or "nothing by mouth") patients. The usual labeled dose is one vial daily in patients greater than 11 years of age (there is a corresponding pediatric drug product, NDA 18-920, which covers the patient population < 11 years of age).

M.V.I.-Adult™ is neither a pharmacy bulk package nor a multi-dose container. The vial 1 and 2 solutions are mixed prior to addition to TPN admixtures by aseptically transferring the contents of vial 1 into vial 2 and mixing. The unit-dose product solutions are mixed prior to addition to a TPN admixture by forcing the plunger-stopper (which separates the two chambers) into the lower chamber (along with the contents of the upper chamber).

The expiration dating period for M.V.I.® Adult is 18 months for the single-dose vials and 15 months for the unit-dose (dual-chambered) vials with refrigerated storage (2-8°C). This expiry is supported by full-time stability data on the previously approved 12-vitamin product, M.V.I.-12® (NDA 8-809), full-time stability data on the presently approved 13-vitamin pediatric product, M.V.I. Pediatric® (NDA 18-920), and 9 months of accelerated (25°C) stability data and associated long-term stability data on three lots each of the single-dose (2-vial kit) and unit-dose (dual chambered vial) presentations of the proposed reformulated M.V.I.® Adult. A larger-than expected loss of vitamin E potency was observed during stability testing of the unit-dose package presentation (approximately _____ loss of initial potency within _____ of storage at 2-8°C). However, the potency assay values were within specified limits after _____ which is only _____ less than the proposed expiration dating period (15 months). On the basis of risk-based review, the vitamin E stability data was found to be acceptable.

**Executive Summary Section****C. Basis for Approvability or Not-Approval Recommendation**

The application is approvable (AE) for the following reasons:

- CMC information for the drug substances is adequate (identical to that approved for NDA's 8-809 and 18-920).
- The drug product manufacturing processes are essentially identical to those approved for NDA's 8-809 and 18-920.
- The components and composition correspond to those listed in the FR notice of April 20th, 2000, and are essentially the same as those for NDA 18-920 (M.V.I. Pediatric).
- The container/closure system is unchanged from that approved for NDA's 8-809 and 18-920.
- The stability data set supports the proposed expiration dating period (15 months for the unit-dose containers and 18 months for the single-dose "kits", which were approved for NDA 8-809).

However, the GMP status of the AstraZeneca Westborough, MA facility is unacceptable as per the EER Summary Report dated September 17th, 2003, attached to the end of this review. In addition, the finished product labeling needs to be revised per DMEDP and ONDC recommendations (listed in the Draft Letter of deficiencies, attached to the end of this review).

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

David Lewis/December 12th, 2003
Mamta Gautam-Basak/Date
Holly Wieland/Date

C. CC Block



65 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

/s/

David Lewis

12/12/03 02:57:16 PM

CHEMIST

The application is approvable pending an acceptable GMP status
and resolution of labeling issues.

Corrected the typos (pages 7, 58, and deficiency letter)

Mamta Gautam-Basak

12/12/03 03:02:38 PM

CHEMIST

Concur

M E M O R A N D U M
S E R V I C E S

DEPARTMENT OF HEALTH AND HUMAN

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 1st, 2003

FROM: David B. Lewis, Ph.D., Chemist, DNDCII, ONDC, co-located with HFD-510 (DMEDP), through Mamta Gautam-Basak, Ph.D., Chemistry Team Leader

SUBJECT: Potential benzo(a)pyrene contamination in dl-alpha tocopheryl acetate bulk vitamin substance (Vitamin E).

TO: NDA 8-809 (M.V.I.-12[®]), NDA 18-920 (M.V.I. Pediatric[®]), and NDA 21-625 (nomenclature pending), aaiPharma, 2320 Scientific Park Drive, Wilmington, NC 28405.

A recent Rapid Alert issued by the Dutch Food and Product Safety Authority advised EU (European Union) members of the limits (maximum 1 ppb) it has imposed on benzo(a)pyrene (BaP) levels in natural Vitamin E in food supplements and food. The Rapid Alert also informed 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). BaP, which is a PAH, is considered to be mutagenic and carcinogenic in animals, and has been limited to a maximum of 1 ppb in consumer products.

According to published literature [*Toxicol. Environ. Chem.* 16:281-94 (1988); *Environ. Sci. Technol.* 26(7): 1278-84 (1992)] the average daily food intake of benzo(a)pyrene is 0.15 µg/kg. Based on an acceptance criterion of 1 ppb contained as an impurity in an adult daily dose (10 mg) or pediatric daily dose (9 mg) of vitamin E, benzo(a)pyrene levels would correspond to 10 and 9 picograms/day respectively. This level of exposure is considerably lower than the average daily food intake of benzo(a)pyrene and suggests that the specification of <1 ppb in vitamin E is reasonable. Although this is supportive, it is unknown if this is was the basis for the Dutch specification limit of < 1 ppb. The cumulative effect of benzo(a)pyrene is unknown in humans, however exposure at these low picogram levels would not be expected to significantly elevate average daily intake of benzo(a)pyrene.

Roche is one of the leading suppliers of natural-source vitamin E, in the form of d-alpha-tocopheryl acetate. Analytical results have shown that vitamin E acetate, as produced by Roche, complies with the recent limits on BaP content imposed by the Dutch authorities. Since Roche is the approved supplier of vitamin E acetate for all of the multiple vitamin injections, which are currently approved (or are being reviewed) in the U.S., the Agency is requesting that the holders of NDA's for multiple vitamin injections verify that batches of vitamin E acetate used in the manufacture of their products comply with the safety limit of 1 ppb of benzo(a)pyrene. This assurance may be accomplished by the inclusion of such test results on every certificate of analysis (COA) for vitamin E acetate. In the absence of such information on the COA, this testing should be performed by the drug product manufacturer and added to the acceptance specifications for the material (vitamin E acetate) received from supplier(s).

Conclusion: It is recommended that every lot of vitamin E acetate (dl-alpha-tocopheryl acetate) used in the manufacturing of approved products should be tested for Benzo(a)pyrene content with an acceptance criterion of "NMT 1 ppb of Benzo(a)pyrene". Batches of Vitamin E acetate may be accepted based on benzo(a)pyrene test results from the supplier, provided that these results are included on the Certificates of Analysis for every received batch of Vitamin E acetate. If the supplier does not perform such testing on every batch of Vitamin E acetate, the NDA holder should perform the testing, either in-house, or via a contract testing facility. The analytical method for Benzo(a)pyrene determination in Vitamin E acetate may be referenced to available literature, or may be provided to the Agency.

Draft Letter to aaiPharma:

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 products (approved NDA's 8-809, M.V.I.-12 and 18-920, M.V.I. Pediatric as well as NDA 21-625, which is currently under review), 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 (addition of a test for benzo(a)pyrene content with an acceptance criterion of NMT 1 ppb) and submit these revised acceptance specifications for Vitamin E acetate to the Agency via CBE supplement.

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

/s/

David Lewis

4/29/03 11:40:15 AM

CHEMIST

Letter to be communicated to the firm.