

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-643

CHEMISTRY REVIEW(S)

2-13-04

NDA 21-643**M.V.I. Adult™ Pharmacy Bulk Package
(Multi-Vitamin Infusion)****aaiPharma****David B. Lewis, Ph.D.
Division of Metabolic and Endocrine Drug Products
(DMEDP, HFD-510)**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	5
The Executive Summary	11
I. Recommendations	11
A. Recommendation and Conclusion on Approvability.....	11
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	11
II. Summary of Chemistry Assessments.....	11
A. Description of the Drug Product(s) and Drug Substance(s)	12
B. Description of How the Drug Product is Intended to be Used.....	13
C. Basis for Approvability or Not-Approval Recommendation	13
III. Administrative.....	14
A. Reviewer's Signature.....	14
B. Endorsement Block	14
C. CC Block.....	14
Chemistry Assessment.....	15
I. DRUG SUBSTANCE	15
1. Description & Characterization	15
a. Description.....	
b. Characterization / Proof Of Structure	
2. Manufacturer	15
3. Synthesis / Method Of Manufacture.....	16
a. Starting Materials - Specs & Tests.....	
b. Solvents, Reagents, etc.....	

c. Flow Chart.....
d. Detailed Description.....
4. Process Controls.....	16
a. Reaction Completion / Other In-Process Tests.....
b. Intermediate Specs & Tests.....
5. Reference Standard	16
a. Preparation.....
b. Specifications.....
6. Regulatory Specifications / Analytical Methods	16
a. Drug Substance Specifications & Tests.....	17
b. Purity Profile.....	17
c. Microbiology.....	17
7. Container/Closure System For Drug Substance Storage.....	17
8. Drug Substance Stability.....	17
II. DRUG PRODUCT.....	17
1. Components/Composition.....	17
2. Specifications & Methods For Drug Product Ingredients	18
a. Active Ingredient(s).....	18
b. Inactive Ingredients	19
3. Manufacturer	19
4. Methods Of Manufacturing And Packaging	19
a. Production Operations.....	19
b. In-Process Controls & Tests.....	19
c. Reprocessing Operations	20
5. Regulatory Specifications And Methods For Drug Product.....	20
a. Sampling Procedures	20
b. Regulatory Specifications And Methods	21
6. Container/Closure System.....	24
7. Microbiology.....	24
8. Drug Product Stability	24
III. INVESTIGATIONAL FORMULATIONS	29

IV. ENVIRONMENTAL ASSESSMENT.....	29
V. METHODS VALIDATION.....	30
VI. LABELING	30
VII. ESTABLISHMENT INSPECTION.....	38 36
VIII. DRAFT DEFICIENCY LETTER.....	37

Chemistry Review Data Sheet

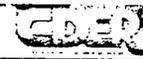
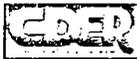
1. NDA 21-643
2. REVIEW #: 1
3. REVIEW DATE: February 11th, 2004
4. REVIEWER: David B. Lewis, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 8-809	APPROVED IN 1953
NDA 21-625 ORIGINAL	27/02/03
NDA 21-625 AMENDMENT	17/04/03
NDA 21-625 CMC Review # 1	12/12/03
NDA 21-625 CMC Review # 2	19/12/03

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
ORIGINAL NDA	17/04/03
AMENDMENT	12/05/03
AMENDMENT	04/06/03
AMENDMENT	11/11/03
AMENDMENT	09/02/04

- The amendment dated May 12th, 2003 provided updated stability data and method validation for the determination of vitamins K and D.
- The amendment dated June 4th, 2003 provided a commitment to submit a CBE supplement regarding benzo(a)pyrene testing for the drug substance, vitamin E acetate.
- The amendment dated November 11th, 2003 provided updated stability data for the drug product.
- The amendment dated February 9th, 2004 provided revised labeling per FDA request.



7. NAME & ADDRESS OF APPLICANT:

Name: AaiPharma
Address: 2320 Scientific Park Drive, Wilmington, NC
28405
Representative: Kevin McKenna, Executive Director, Regulatory
Affairs, AstraZeneca*
Telephone: (302) 886-2742 (phone), (302) 886-2822 (FAX)

* AstraZeneca is the authorized U.S. Agent for aaiPharma regarding this application.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: M.V.I. Adult™ Pharmacy Bulk Pack (Multi-Vitamin Infusion)
- b) Non-Proprietary Name (USAN): Multi-Vitamin Infusion
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), based on NDA 8-809, M.V.I.-12® (aaiPharma).

10. PHARMACOL. CATEGORY: Nutritional Large Volume Parenteral (LVP)

11. DOSAGE FORM: Injection

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: The drug product contains the following drug substances (expressed as amount per 10 mL dose):

- Vitamin C (ascorbic acid, USP), 200 mg
- Vitamin A, USP (retinol), 1 mg (3,300 USP units)
- Vitamin D (ergocalciferol, USP), 5 mcg (200 USP Units)
- Vitamin B₁ (thiamine hydrochloride, USP), 6 mg
- Vitamin B₂ (riboflavin 5-phosphate sodium, USP), 3.6 mg
- Vitamin B₆ (pyridoxine hydrochloride, USP), 6 mg
- Niacinamide, USP, 40 mg
- Dexpanthenol, USP, 15 mg
- Vitamin E, USP (*dl*-alpha-tocopheryl acetate), 10 mg
- Vitamin K (phylloquinone, phytonadione, USP), 150 mcg
- Biotin, USP, 60 mcg
- Folic acid, USP, 600 mcg
- Vitamin B₁₂ (cyanocobalamin, USP), 5 mcg

13. ROUTE OF ADMINISTRATION: Intravenous (I.V.)

14. Rx/OTC DISPENSED: Rx OTC

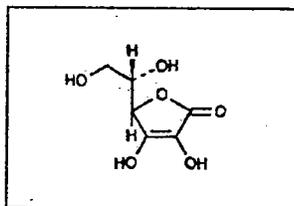
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

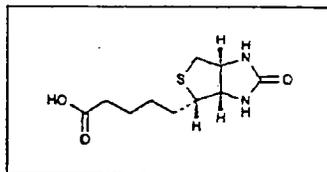
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

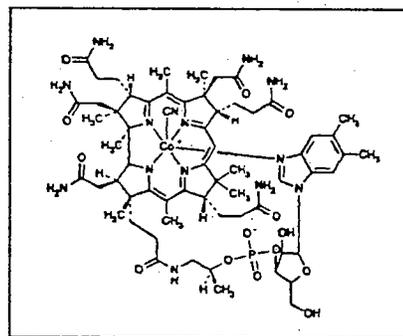


Chemistry Review Data Sheet

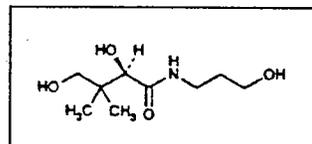
- Biotin, $C_{10}H_{16}N_2O_3S$, 244.31 g/mol



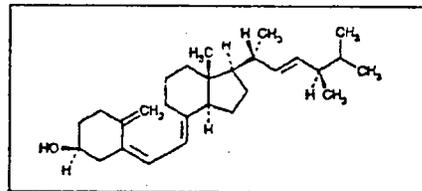
- Cyanocobalamin, $C_{63}H_{88}CoN_{14}O_{14}P$, 1355.37 g/mol
(Vitamin B₁₂)



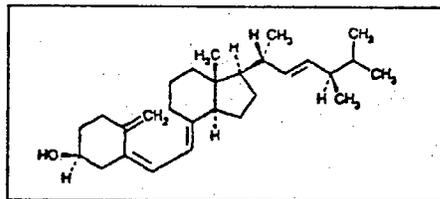
- Dexpanthenol, $C_9H_{19}NO_4$, 205.25 g/mol



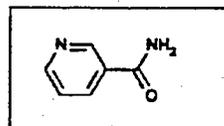
- Ergocalciferol, $C_{28}H_{44}O$, 396.65 g/mol
(Vitamin D₂)



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

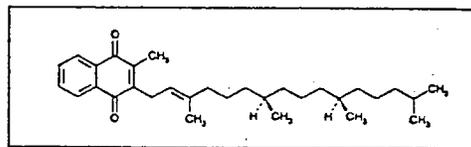


- Niacinamide, $C_6H_6N_2O$, 122.12 g/mol

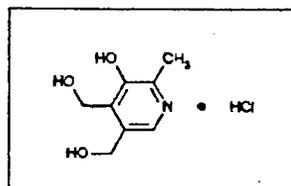


Chemistry Review Data Sheet

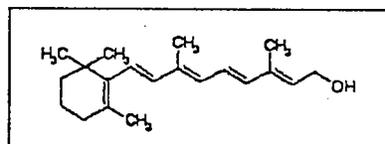
- Phylloquinone, $C_{31}H_{46}O_2$, 450.70 g/mol
(Vitamin K₁, phytonadione)



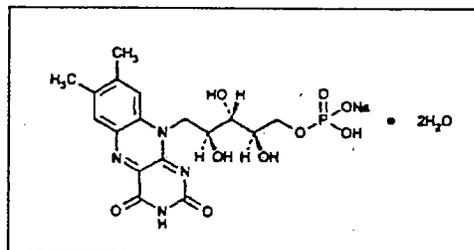
- Pyridoxine•HCl, $C_8H_{11}NO_3 \cdot HCl$, 205.64 g/mol
(Vitamin B₆)



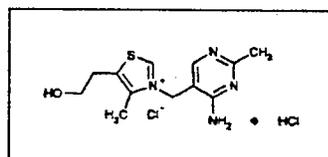
- Retinol, $C_{20}H_{30}O$, 286 g/mol
(Vitamin A)



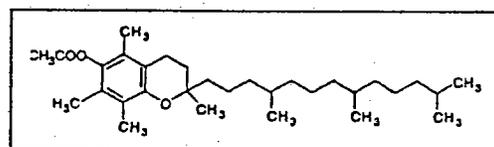
- Riboflavin 5'-phosphate sodium, $C_{17}H_{20}N_4NaO_9P \cdot 2H_2O$, 514.36 g/mol
(Vitamin B₂)



- Thiamine hydrochloride, $C_{12}H_{17}ClN_4OS \cdot HCl$, 337.27 g/mol
(Vitamin B₁)



- *dl*- α -tocopheryl acetate, $C_{31}H_{52}O_3$, 472.8 g/mol
(Vitamin E)



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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

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: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	22/12/03	J. D'Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	ACCEPTABLE*		
Methods Validation	Post-approval		
ODS	NOT ACCEPTABLE**		
EA	ACCEPTABLE	5/01/04	D. Lewis, Ph.D.
Microbiology	ACCEPTABLE	27/08/03	P. Stinavage, Ph.D.

* 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 21-643

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommended for APPROVAL from the standpoint of CMC pending submission of adequate labeling (see labeling-related deficiencies).

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

The NDA sponsor has agreed to submit a CBE-30 supplement providing verification that benzo(a)pyrene levels in the drug substance, vitamin E acetate are less than 1 ppb.

II. Summary of Chemistry Assessments

NDA 21-643 covers the pharmacy bulk packaged (PBP) version of M.V.I. Adult™ (multi-vitamin infusion), submitted under NDA 21-625, approved on January 30th, 2004. M.V.I. Adult™ (formerly M.V.I.-12®) was originally filed under NDA 8-809; *this NDA covered the single-dose and PBP package presentations*. M.V.I.-12® was reformulated per the Federal Register Notice of April 20th, 2000 (65 FR 21200), and the reformulated product was filed under NDA 21-625 with the proprietary name of M.V.I. Adult™ (the reformulated product contained thirteen vitamin substances, with the addition of Vitamin K). However, due to the CDER bundling policy, the PBP package presentation was split off into its own NDA (NDA 21-643). The Chemistry, manufacturing and controls information (CMC) for the PBP package presentation of the reformulated multi-vitamin infusion was initially provided in NDA 21-625, but was split off into this NDA (21-643) per FDA request on April 17th, 2003. CMC information for the PBP package presentation is contained in original NDA 21-625 (submission dated February 27th, 2003, Vols. 1 and 2), in original NDA 21-643 (April 17th, 2003), and in subsequent amendments to NDA 21-643 (May 12th, June 4th, November 11th, 2003 and February 9th, 2004). The April 17th, 2003 submission refers to sections of original NDA 21-625 for CMC for this NDA. *The qualitative and quantitative composition of the NDA 21-643 drug product is identical to that for M.V.I. Adult (NDA 21-625)*, and corresponds to the composition for adult multi-vitamin injections, which was defined in 65 FR 21200. It should be noted that the original 12-vitamin adult formulation will still be marketed under NDA 8-809 (with reformulated amounts of ascorbic acid, pyridoxine, thiamine, and folic acid) per sponsor request and with FDA concurrence.

Executive Summary Section

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

The drug product has the proprietary name of M.V.I. Adult™. The drug product nomenclature was submitted to the Office of Drug Safety (ODS) under NDA 21-625 (single-dose product), since the proprietary and established names are pertinent for both the single-dose product (NDA 21-625) and the pharmacy bulk package (this NDA). ODS reviewed the nomenclature and found the proposed proprietary & established names unacceptable due to similarity between the nomenclature for the reformulated 13-vitamin adult product (NDA's 21-625 and 21-643) and the reformulated 12-vitamin adult product (NDA 8-809). However, DMEDP, ONDC, and the Labeling and Nomenclature Committee (LNC) agreed that the proprietary & established names for NDA's 21-625 and 21-643 could remain as proposed: M.V.I. Adult™ (multi-vitamin infusion) if the established name for the reformulated 12-vitamin adult preparation (NDA 8-809) was changed to "multi-vitamin infusion without vitamin K". Since this solution was also proposed by the sponsor, agreement between the Agency and the sponsor is not a problem. The drug product is a Pharmacy Bulk Packaged (PBP) sterile injection and is provided as two 50-mL glass doses, which are contained in a 50-mL glass vial (Vial 1) and a 50-mL glass vial (Vial # 2), which are both closed with stoppers. The PBP contains ten (10) 10-mL doses of the drug product; a complete dose comprises 5 mL each of the Vial 1 and 2 solutions. Vial 1 contains ten (10) vitamin substances: retinol (Vitamin A, USP), ergocalciferol, USP (Vitamin D₂), *dl*- α -tocopheryl acetate (Vitamin E, USP), phylloquinone (phytonadione, USP, or Vitamin K₁), ascorbic acid, USP (Vitamin C), niacinamide, USP, riboflavin 5-phosphate sodium, USP (Vitamin B₂), thiamine hydrochloride, USP (Vitamin B₁), pyridoxine hydrochloride, USP (Vitamin B₆), and dextranthenol, USP. Vial 2 contains three (3) vitamin substances: biotin, USP, folic acid, USP, and cyanocobalamin, USP (Vitamin B₁₂). The formula quantity of each vitamin substances corresponds to the defined composition from the Federal Register Notice of April 20th, 2000 (65 FR 21200).

None of these vitamins are manufactured under drug GMP conditions, having been classified as foods (nutritional materials). The vitamin substances are tested to the requirements of the current USP monographs, and are also tested for bioburden and bacterial endotoxins. *The CMC information for the vitamin substances was reviewed and found adequate to support NDA 21-625, and is adequate to support this NDA.*

The manufacture of the drug product solutions is identical to that for the unit-dose and 2-vial package presentations of M.V.I. Adult™, which was reviewed and found adequate for NDA 21-625. The filling processes are also identical (— which was addressed in the Microbiology review, and found adequate for this NDA). The container/closure system is unchanged from that, which is presently used (and approved) under NDA 8-809.

Executive Summary Section

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

The drug product described in this NDA is a Pharmacy Bulk Package, consisting of two 50-mL solutions, each providing ten 5-mL doses. The Vial 1 (10-vitamin) solution is packaged in a 50-mL vial, and the Vial 2 (3-vitamin) solution is packaged in a $\frac{1}{2}$ vial. In order to prepare the finished dosage form, the contents of Vial 1 are transferred to Vial 2, forming a $\frac{1}{2}$ 13-vitamin solution. One complete dose of M.V.I. Adult™ (multi-vitamin infusion) consists of 5 mL each of the Vial 1 and 2 solutions (10-mL dose). These 10-mL doses are removed from Vial 2 in a "suitable work area" such as a laminar flow hood and added to TPN admixtures. The closures for Vials 1 and 2 may only be penetrated once, and any unused contents must be discarded within 4 hours after the closure is penetrated. The typical dosing schedule is one 10-mL dose (5 mL each of Vial 1 and 2 solutions, combined) once daily as part of a Total Parenteral Nutritional (TPN) admixture, to be administered to adults and children over the age of 11 years (the drug product is diluted into a mixture of other nutritional LVP and SVP drug products, including dextrose, amino acid, and electrolyte injection). The formula quantities of the thirteen (13) vitamins contained in M.V.I. Adult™ are defined by 65 FR 21200 (Federal Register Notice dated April 20th, 2000), and are provided in this review on the cover pages (Item 12), and in the Chemistry Assessment (Section II.1, Drug Product components and composition). The proposed expiration dating period is 18 months with refrigerated storage (2-8°C, as defined in ICH Q1A). This expiry is supported by 6 months of accelerated (25°C/60% RH) and twelve months of long-term (2-8°C) stability data on three lots of M.V.I. Adult™ (Multi-vitamin infusion) and by full-time stability data for many lots of the previously approved drug product, M.V.I.-12® (Multi-vitamin infusion, filed under NDA 8-809).

C. Basis for Approvability or Not-Approval Recommendation

The application may be approved from the standpoint of chemistry, manufacturing and controls (CMC) on the basis of the following:

- Adequate information regarding raw material controls (per reference to approved NDA's 8-809, 18-920, and 21-625).
- Adequate information regarding drug product manufacture (per reference to approved NDA 21-625).
- Adequate stability data to support the proposed 18-month shelf life (refrigerated conditions); this data included accelerated and long-term stability submitted for the NDA 21-643 product (PBP package presentation), and reference to approved NDA 21-625 for full-term stability data on the single-dose version of the same drug product.
- Acceptable cGMP status for the manufacturing and testing facilities.
- Acceptable labeling for the drug product.

Note: The bulk vitamin manufacturing facilities were not inspected for drug cGMP compliance, because vitamins are considered to be foods, and are not subject to drug GMP's.

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

ChemistName/Date: David Lewis/February 11th, 2004

ChemistryTeamLeaderName/Date: Mamta Gautam-Basak/February 11th, 2004

ProjectManagerName/Date: Holly Wieland

C. CC Block

23 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-_____

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
2/13/04 12:37:05 PM
CHEMIST

The application may be approved from the standpoint of CMC.
I corrected the date of the last amendment to
February 9th throughout the review (cover sheet, executive
summary section, labeling section, and draft deficiency letter
outcome section).

Mamta Gautam-Basak
2/13/04 01:01:59 PM
CHEMIST
Concur