

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-559

CHEMISTRY REVIEW(S)



NDA 21-559

Infuvite Adult

Sabex, Inc.

**David B. Lewis, Ph.D.
Division of Metabolic and Endocrine Drug Products
(DMEDP, HFD-510)**

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VIII. DRAFT DEFICIENCY LETTER None

**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Review Data Sheet

1. NDA 21-559

2. REVIEW #: 1

3. REVIEW DATE: May 20, 2003

4. REVIEWER: David B. Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 21-163	19/07/99
NDA 21-163/S-002	08/02/01

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
ORIGINAL NDA	14/08/02
AMENDMENT	29/10/02
AMENDMENT	10/03/03
AMENDMENT	10/03/03
AMENDMENT	29/04/03
AMENDMENT	16/05/03

- The amendment dated October 29th, 2002 provides revised labeling for NDA 21-559.
- The amendment dated March 10th, 2003 provides updated primary stability data for INFUVITE ADULT
- The amendment dated March 10th, 2003 was filed to NDA 21-163 (INFUVITE ADULT single-dose), and provides full-term long-term ICH stability data for the single-dose drug product. This data serves as supportive stability data for INFUVITE ADULT



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- Cholecalciferol (Vitamin D₃): 40 IU per mL, 200 IU per dose
- Thiamine•HCl (Vitamin B₁): 1.2 mg per mL, 6 mg per dose
- Riboflavin 5'-phosphate sodium (Vitamin B₂): 0.72 mg per mL, 3.6 mg per dose
- Niacinamide: 8 mg per mL, 40 mg per dose
- Pyridoxine•HCl (Vitamin B₆): 1.2 mg per mL, 6 mg per dose
- Dexpantenol: 3 mg per mL, 15 mg per dose
- *dl*- α -tocopheryl acetate (Vitamin E): 2 IU per mL, 10 IU per dose
- Phytonadione (Vitamin K₁): 0.03 mg (30 μ g) per mL, 0.15 mg (150 μ g) per dose
- Folic acid: 120 μ g per mL, 600 μ g per dose
- Biotin: 12 μ g per mL, 60 μ g per dose
- Cyanocobalamin (Vitamin B₁₂): 1 μ g per mL, 5 μ g per dose

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

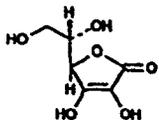
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed

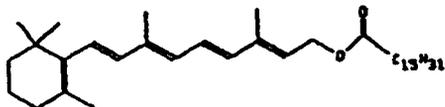
 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: The drug product contains the following thirteen (13) vitamin drug substances:

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



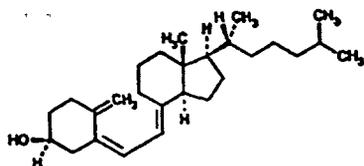
- Retinyl palmitate (Vitamin A, USP), C₃₆H₆₀O₂, 524.9 g/mol



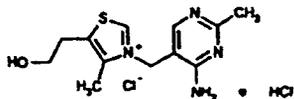
- Cholecalciferol, USP (Vitamin D₃), C₂₇H₄₄O, 384.6 g/mol

CHEMISTRY REVIEW

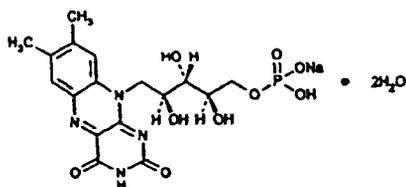
Chemistry Review Data Sheet



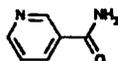
- Thiamine Hydrochloride, USP (Vitamin B₁), C₁₂H₁₇ClN₄OS•HCl, 337.27 g/mol



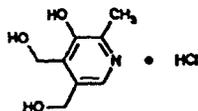
- Riboflavin 5'-Phosphate Sodium, USP (Vitamin B₂), C₁₇H₂₀N₄NaO₉P•2H₂O, 514.36 g/mol



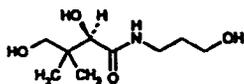
- Niacinamide, USP, C₆H₆N₂O, 122.12 g/mol



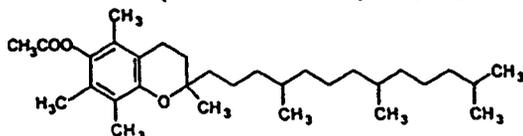
- Pyridoxine Hydrochloride, USP (Vitamin B₆), C₈H₁₁NO₃•HCl, 205.64 g/mol



- Dexpanthenol, USP (Vitamin B₅), C₉H₁₉NO₄, 205.25 g/mol



- *dl*-α-tocopherol acetate (Vitamin E, USP), C₃₁H₅₂O₃, 472.76 g/mol



- Phytonadione, USP (Vitamin K₁), C₃₁H₄₆O₂, 450.70 g/mol



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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
CMC Amendment	21-163, N-000, C	Updated stability data
Memorandum to File	21-559 Memorandum dated April 1 st , 2003	European Rapid Alert – warning about benzo(a)pyrene in Vitamin E acetate

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	07/05/03	J. D'Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
ODS	Submitted consult request 2-13-03, pending		
EA	ACCEPTABLE*		D. Lewis
Microbiology	ACCEPTABLE	29/01/03	P. Stinavage

* A categorical exclusion was granted per 21 CFR 25.31, sections (b) and (c) in sNDA 21-163/SCM-002. This exclusion is pertinent to this NDA, since the drug product solutions for NDA 21-559 are identical to those for NDA 21-163.

Executive Summary Section

combined by transferring the vial 1 solution into vial 2 before dispensing. The drug product is an _____ sterile solution. The composition of the drug product complies with the requirements provided in the Federal Register Notice dated April 20th, 2000 (65 FR 21200). The manufacturing processes, control procedures, and facilities for INFUVITE ADULT _____ are identical to those approved for the single-dose version (NDA 21-163/S-002). The manufacturing site for the drug product found ACCEPTABLE regarding cGMP status. Issues of sterility assurance were addressed in the microbiology review, and found adequate to support this NDA.

All of the vitamin substances comply with the corresponding USP monograph requirements. The individual bulk vitamins are also tested for bioburden and endotoxins to support their use in a parenteral drug product. This NDA refers to NDA 21-163 and sNDA 21-163/S-002 for CMC information on the drug substances; this information is adequate.

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

The drug product is intended for use as a Pharmacy Bulk Package (PBP), with intended ten 10-mL doses per vial. Vials 1 and 2 must be combined in order to form the complete drug product, with the contents of Vial 1 being removed via syringe and transferred to Vial 2 for mixing; the combined vial 1 and 2 solutions comprise the finished drug product. After mixing the contents of Vials 1 and 2, 10-mL doses are removed and dispensed into total parenteral admixtures (TPN). The closure may only be punctured one time, so any solution remaining after the TPN admixture preparation is discarded. INFUVITE ADULT _____

_____ is intended for use as a total parenteral nutrition (TPN) additive. The usual daily dose of INFUVITE ADULT (multiple vitamins for infusion) is one 10-mL vial; to be added directly to NLT 500 mL, and preferably 1,000 mL of IV dextrose, saline, or similar infusion solutions. The proposed expiration dating period for the drug product is _____, with storage at 2-8°C (refrigerator storage); this shelf life is supported by _____ accelerated (25°C/60% RH) stability data and _____ of long-term (2-8°C) stability data on _____ lots apiece of INFUVITE ADULT _____ Vials 1 & 2, along with _____ of long-term (2-8°C) stability data for _____ lots of Vials 1 and 2 of INFUVITE ADULT, single-dose (NDA 21-163).

C. Basis for Approvability or Not-Approval Recommendation

INFUVITE ADULT single-dose has an identical formulation as the pharmacy bulk packaged presentation, and is filled into a smaller version of the same container (USP Type I glass vials). There are no deficiencies regarding the manufacture, packaging, or specifications for the drug product. The labeling has been revised in order to comply with the requirements for a Pharmacy Bulk Package. The acceptance specification for the bulk vitamin drug substance, dl-alpha-tocopheryl acetate needs to be revised to include a test for benzo(a)pyrene content with an acceptance criterion of "NMT 1 ppb"; this may be accomplished post-approval via CBE-0 supplement.



Executive Summary Section

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement Block: N/A (filed through DFS)

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

**APPEARS THIS WAY
ON ORIGINAL**

33 Page(s) Withheld

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**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

5/22/03 11:46:57 AM

CHEMIST

Updated and submitted for David Lewis in his absence

Mamta Gautam-Basak

5/22/03 11:51:18 AM

CHEMIST

Concur with review

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 21559/000	Action Goal:	
Stamp:	16-AUG-2002	District Goal:	17-APR-2003
Regulatory Due:	16-JUN-2003	Brand Name:	INFUVITE ADULT PHARMACY
Applicant:	SABEX 2002 INC	Estab. Name:	BULK PKG
	NO CITY, , XX	Generic Name:	MULTIPLE VITAMINS FOR INFUSION
	3S	Dosage Form:	(INJECTION)
Priority:	510	Strength:	N/A
Org Code:			

Application Comment: NDA 21-559 PROVIDES CMC INFORMATION FOR INFUVITE ADULT WHICH IS A PHARMACY BULK PACKAGE VERSION OF NDA 21-163 (INFUVITE ADULT). NDA 21-163 PROVIDED SINGLE-DOSE CONTAINERS. THE DRUG PRODUCT IS AN SMALL VOLUME PARENTERAL INJECTION INTENDED FOR USE AS A TPN ADDITIVE. THE DRUG SUBSTANCES ARE ALL BULK VITAMINS, WHICH ARE DUAL PURPOSE MATERIALS (FOOD/NUTRITIONAL & DRUG SUBSTANCES) AND ARE NOT MANUFACTURED USING GMP'S AND ARE NOT SUBJECT TO CURRENTLY MAINTAINED DMF'S. INSPECTION IS NOT BEING REQUESTED OF THE DRUG (VITAMIN) SUBSTANCE MANUFACTURERS; CMC INFORMATION ON THE VITAMINS IS REFERENCED TO NDA'S 21-163 AND 21-265 (SABEX INFUVITE ADULT AND INFUVITA PEDIATRIC). (on 20-SEP-2002 by D. LEWIS (HFD-510) 301-827-6420)

FDA Contacts: S. MCCORT (HFD-510) 301-827-6415 , Project Manager
D. LEWIS (HFD-510) 301-827-6420 , Review Chemist
S. MARKOVSKY (HFD-510) 301-827-6420 , Team Leader

Overall Recommendation: ACCEPTABLE on 01-OCT-2002 by J. D AMBROGIO (HFD-322) 301-827-9054

Establishment: CFN 9615155 FEI 3000280957
SABEX
145 JULES-LEGER STREET
BOUCHERVILLE, QC, , CA j4b 7k8

DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: SVS OAI Status: NONE

Estab. Comment: THE SABEX FACILITY IS USED FOR MANUFACTURE (STERILE, PACKAGING, AND LABELING OF THE DRUG PRODUCT. THIS FACILITY IS ALSO USED FOR MANUFACTURE OF THE FDA-APPROVED RELATED DRUG PRODUCTS INFUVITE PEDIATRIC (NDA 21-265) AND INFUVITE ADULT (NDA 21-163). (on 20-SEP-2002 by D. LEWIS (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-SEP-2002				LEWIS
MITTED TO DO	23-SEP-2002	GMP			DAMBROGIOJ
RECOMMENDATION	01-OCT-2002			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

OC RECOMMENDATION

01-OCT-2002

ACCEPTABLE

DAMBROGIOJ

DISTRICT RECOMMENDATION

APPEARS THIS WAY
ON ORIGINAL