

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-646

CHEMISTRY REVIEW(S)

NDA 21-646

Infuvite Pediatric Pharmacy Bulk Package

Sabex 2002 Inc.

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Department of Metabolic and Endocrine Drug Products
DMEDP (HFD-510)



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1. NDA 21-646
2. REVIEW #: 1
3. REVIEW DATE: January 22nd, 2004
4. REVIEWER: David B. Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL NDA 21-265	20/04/00
ORIGINAL NDA 21-559	14/08/02

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
ORIGINAL NDA 21-646	31/03/03
AMENDMENT 1	13/05/03
AMENDMENT 4	29/10/03
AMENDMENT 5	26/11/03
AMENDMENT 6	11/12/03
AMENDMENT 8	15/12/03
AMENDMENT 9	12/01/04

- Amendment 1 provided clarification for the various analytical testing facilities for the drug substances and the drug product.
- Amendment 4 provided for a change to the maximum intended batch size for Vial 1 and 2 solutions.
- Amendment 5 provided an alternate testing facility.
- Amendment 6 provided revised labeling and aluminum determination data

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- Amendment 8 provided supplier's COA's for Vitamin E acetate containing test results for benzo(a)pyrene.
- Amendment 9 provided revised labeling and stability specifications and updated stability data per FDA request.
- Amendments 2, 3, and 7 did not contain CMC input, and were not addressed in this review.

7. NAME & ADDRESS OF APPLICANT:

Name: Sabex 2002 Inc. (Sabex Pharmaceutical Products)
Address: 145 Jules-L•ger, Boucherville, QC, CANADA
J48 7K8
Representative: Leonor Ferreira, Director Regulatory Affairs
Telephone: (450) 641-4903 (X2161) Phone
(514) 596-1460 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: INFUVITE PEDIATRIC Pharmacy Bulk Package
- b) Non-Proprietary Name (USAN): Multiple Vitamins for Infusion
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2). The reference listed drug is NDA 21-265

10. PHARMACOL. CATEGORY: Nutritional LVP

11. DOSAGE FORM: Injection

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12. **STRENGTH/POTENCY:** The drug product contains the following drug substances (strength expressed per 5-mL dose, 4 mL from Vial 1 and 1 mL from Vial 2):

- Ascorbic acid, USP (Vitamin C): 80 mg
- Retinol palmitate (Vitamin A, USP): 2,300 IU (0.7 mg)
- Cholecalciferol, USP (Vitamin D₃): 400 IU (10 µg)
- Thiamine hydrochloride, USP (Vitamin B₁): 1.2 mg
- Riboflavin 5-phosphate sodium, USP (Vitamin B₂): 1.4 mg
- Pyridoxine hydrochloride, USP (Vitamin B₆): 1 mg
- Niacinamide, USP: 17 mg
- Dextranthenol, USP (as *d*-pantothenyl alcohol): 5 mg
- *dl*-alpha-tocopheryl acetate (Vitamin E, USP): 7 IU (7 mg)
- Phytonadione, USP (Vitamin K₁): 0.2 mg
- Folic acid, USP: 140 mcg
- Biotin, USP: 20 mcg
- Cyanocobalamin, USP (Vitamin B₁₂): 1 mcg

13. **ROUTE OF ADMINISTRATION:** Intravenous infusion

14. **Rx/OTC DISPENSED:** Rx OTC

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

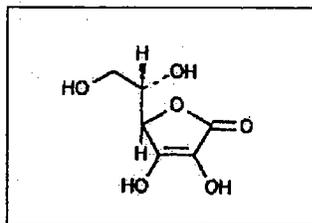
SPOTS product – Form Completed

Not a SPOTS product

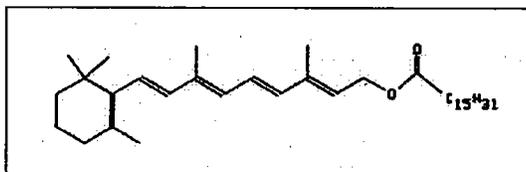
Chemistry Review Data Sheet

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

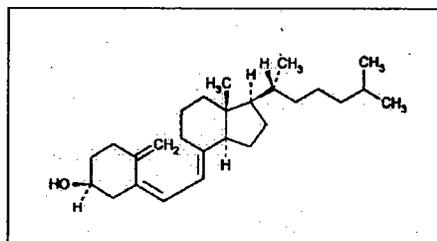
- Ascorbic acid, USP
 $C_6H_8O_6$ (176.12 g/mol)
 (Vitamin C)



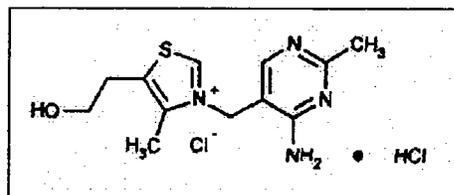
- Retinyl palmitate
 $C_{36}H_{60}O_2$, 524.88 g/mol
 (Vitamin A, USP)



- Cholecalciferol, USP
 $C_{27}H_{44}O$, 384.64 g/mol
 (Vitamin D₃), $C_{27}H_{44}O$



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



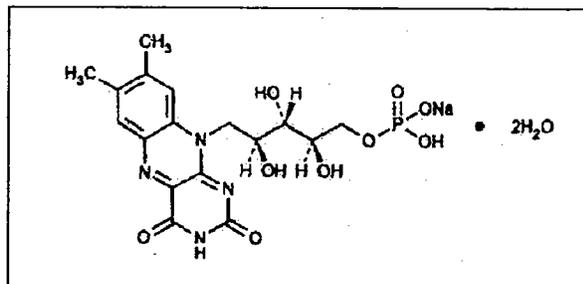


CHEMISTRY REVIEW

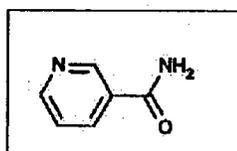


Chemistry Review Data Sheet

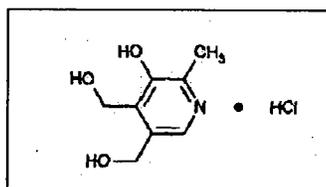
- Riboflavin 5'-Phosphate Sodium, USP
 $C_{17}H_{20}N_4NaO_9P \cdot 2H_2O$, 514.36 g/mol
(Vitamin B₂)
CHECK



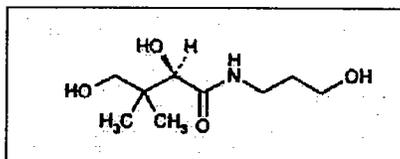
- Niacinamide, USP
 $C_6H_6N_2O$, 122.12 g/mol



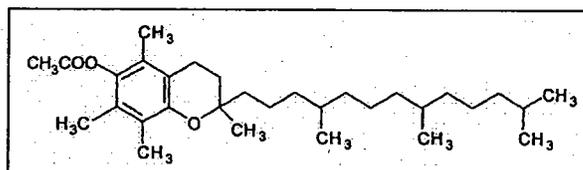
- Pyridoxine Hydrochloride, USP
 $C_8H_{11}NO_3 \cdot HCl$, 205.64 g/mol
(Vitamin B₆)



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



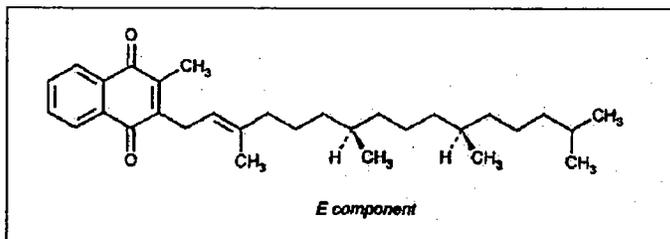
- *dl*- α -tocopherol acetate
 $C_{31}H_{52}O_3$, 472.76 g/mol
(Vitamin E, USP)



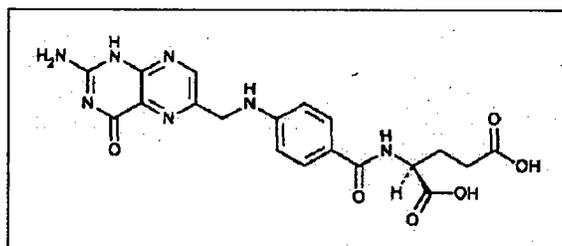


Chemistry Review Data Sheet

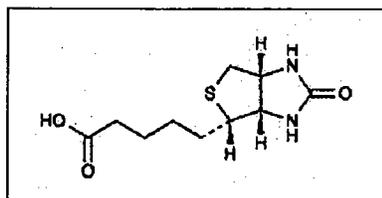
- Phytonadione, USP
 $C_{31}H_{46}O_2$, 450.70 g/mol
(Vitamin K_1)



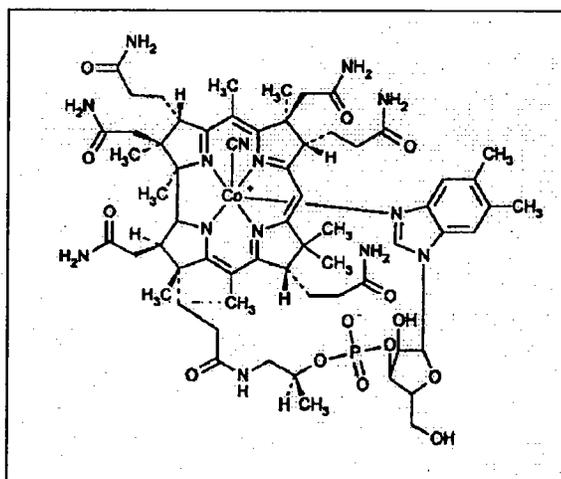
- Folic acid, USP
 $C_{19}H_{19}N_7O_6$, 441.40 g/mol



- 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 B_{12})



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	III			3	Adequate	30/01/03	
	II			3	Adequate	16/12/98	

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	07/01/04	S. Adams
Pharm/Tox	N/A		
Methods Validation	Pending approval		
ODS	Not adequate*	16/05/03	M. Lee, Pharm. D.
LNC	N/A		
EA	Adequate	09/01/04	D. Lewis, Ph.D.**
Microbiology	Adequate	24/09/03	P. Stinavage, Ph.D.

* Revised Labeling was submitted following communication of labeling deficiencies to the NDA sponsor. The ODS consult review covered NDA's 21-559 and this NDA

** Referred to NDA 21-265 (Categorical Exclusion)



The Chemistry Review for NDA 21-646

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from the standpoint of chemistry, manufacturing and controls.

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

Compatibility studies should be performed to support the label claim that TPN admixtures containing INFUVITE ADULT drug products are stable for 24 hours after preparation. These studies may be conducted as a post-approval Phase 4 Commitment, with the study protocol, methods, and results to be submitted to the Agency within 1 year of approval of NDA 21-646. This information should be submitted to the Agency as a Changes Being Effected (CBE-0) supplemental application. The results obtained for the related NDA 21-559 (INFUVITE ADULT PHARMACY BULK PACKAGE) may be submitted in support of this NDA 21-646.

II. Summary of Chemistry Assessments

NDA 21-646 provides chemistry, manufacturing and controls (CMC) information for INFUVITE PEDIATRIC Pharmacy Bulk Package which is the pharmacy bulk packaged (PBP) version of the approved NDA 21-265 (INFUVITE PEDIATRIC). NDA 21-265 describes a single-dose drug product. Both NDA 21-646 and 21-265 INFUVITE PEDIATRIC drug products are provided as 2-vial "kits", which require combining before dispensing and use. The drug product solutions for NDA's 21-265 and 21-646 are identical, as are all of the thirteen bulk vitamin drug substances for the drug product. The drug product described in this NDA (PBP package presentation) would have been filed *via* prior-approval supplement (to NDA 21-265), but was "split off" into its own NDA (this NDA, 21-646) due to the CDER bundling policy, which requires PBP package presentations to be filed under separate NDA's.

CMC information for NDA 21-646 was provided in the original NDA, dated March 31st, 2003 (with references to original NDA 21-265), and in the amendments dated May 13th, October 29th, November 26th, December 11th, December 15th, 2003 and January 12th, 2004. All of the manufacturing and testing facilities for the drug product were found acceptable by the Office of Compliance (OC).

Executive Summary Section

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

The drug product, INFUVITE PEDIATRIC Pharmacy Bulk Package (multiple vitamins for infusion) is a pharmacy bulk packaged (PBP) multi-vitamin injection intended for use as a total parenteral nutritional (TPN) additive in pediatric patients (up to 11 years of age). The drug product consists of two vials, designated Vial 1 and Vial 2. Each 2-vial kit provides ten (10) 5-mL single doses of the drug product. Vial 1 contains 40 mL of a solution of ten (10) vitamin substances in a 50-mL vial and Vial 2 contains 10 mL of a solution of three (3) vitamin substances in a 10-mL vial. The Vial 1 vitamin substances are ascorbic acid (Vitamin C), retinyl palmitate (Vitamin A), cholecalciferol (Vitamin D₃), thiamine•HCl (Vitamin B₁), riboflavin 5-phosphate sodium (Vitamin B₂), pyridoxine•HCl (Vitamin B₆), niacinamide, dexpanthenol, *dl*- α -tocopheryl acetate (Vitamin E), and phytonadione (Vitamin K₁). The Vial 2 vitamin substances are folic acid, biotin, and cyanocobalamin (Vitamin B₁₂). The drug product is sterile. The components and composition for INFUVITE PEDIATRIC PBP are identical to those approved for INFUVITE PEDIATRIC single-dose presentation (NDA 21-265). The package presentation for INFUVITE PEDIATRIC PBP is identical to that for INFUVITE ADULT PBP (NDA 21-559).

All of the thirteen (13) drug substances in INFUVITE PEDIATRIC comply with the requirements of the current USP monographs (all 13 substances are compendial). CMC information for the drug substances are referred to NDA 21-265 (INFUVITE PEDIATRIC, single-dose product); this information was found adequate to support NDA 21-265, and is also adequate to support this NDA.

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

The drug product is intended for use as a *pharmacy bulk package* (as described in the current USP, general Chapter <1>). The drug product is supplied as a 2-vial “kit”, with Vial 1 containing 40 mL of solution in a 50-mL vial and Vial 2 containing 10 mL of solution in a 10-mL vial. The contents of Vial 2 are withdrawn and injected into Vial 1 prior to use; then, the combined drug product (Vial 1 and 2 solutions) are dispensed to several (up to 10) TPN admixtures in a laminar flow hood. The closure for Vial 1 is penetrated only once, per PBP requirements (USP Chapter <1>). The typical dosing schedule for INFUVITE PEDIATRIC is once daily (as a component of a TPN admixture); INFUVITE PEDIATRIC Pharmacy Bulk Package is not for direct infusion.

The proposed expiration dating period for INFUVITE PEDIATRIC Pharmacy Bulk Package is 18 months with refrigerated storage (2-8°C, 36-46°F). This expiry is supported by full-term (18 months plus) stability data for INFUVITE PEDIATRIC (single-dose package presentation, many commercial lots) along with three months of accelerated (25°C/60% RH) stability data on three lots each of Vials 1 and 2 accompanied by long-term stability data (2-8°C) on the same exhibit lots. The stability studies for the PBP are ongoing.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The application may be approved on the basis of acceptable CMC information for drug product manufacture and control along with acceptable labeling & nomenclature. The stability data submitted in support of this application, coupled with the accumulated stability data for the related NDA, 21-265 support the proposed expiration dating period of 18 months at 2-8°C. In addition, the following points were noted:

- The manufacturing processes for INFUVITE PEDIATRIC Pharmacy Bulk Package (NDA 21-646) are essentially identical to those approved for INFUVITE PEDIATRIC (single dose product, NDA 21-265), and those approved for INFUVITE ADULT Pharmacy Bulk Package (NDA 21-559).
- All of the drug substances comply with current USP monograph requirements.
- The regulatory specifications were essentially identical to those approved for INFUVITE PEDIATRIC single-dose presentation (NDA 21-265); the tests, analytical methods, and acceptance criteria for this NDA are the same as those approved for NDA 21-265.
- The manufacturing and testing facilities for the drug product were found acceptable by the Office of Compliance (OC) regarding current GMP status.

Note: Bulk vitamins are not manufactured under cGMP conditions, and are not described in current drug master files. Instead, these materials are accepted as food-grade materials, and are further tested for bioburden and endotoxins. The drug substance manufacturing facilities were not included in the EES (inspection) request, since these materials are considered to be foods.

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

D. Lewis/Date: Same date as draft review

M. Gautam-Basak/Date

H. Wieland/Date

C. CC Block

25 Page(s) Withheld

4 § 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

1/22/04 10:01:57 AM

CHEMIST

This application may be approved from the standpoint of
chemistry, manufacturing and controls.

Changed the review date to January 22nd. The table
of contents is correct.

Mamta Gautam-Basak

1/22/04 02:49:05 PM

CHEMIST

Concur