CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-163

CHEMISTRY REVIEW(S)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-163 **DATE REVIEWED:** 4-14-00

REVIEW #: 2 **REVIEWER:** David B. Lewis, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	07-19-99	07-20-99	07-29-99
AMENDMENT	FAXed on 04-11-00		

NAME & ADDRESS OF APPLICANT: SABEX Pharmaceutical Products (Produits Pharmaceutiques)
145 Jules-Leger, Boucherville, PQ, CANADA J4B 7K8
Phone: (450)-641-4903
FAX: (514) 596-1460
Ms. Leonor Ferreira, M.Sc., MBA

Authorized U.S. Agent: Ken Muhvich, Ph.D.
2929 Circle Road
Ruxton, MD 21204

DRUG PRODUCT NAME

Proprietary:	Multi-12®
Established:	Multiple Vitamins for infusion
Code Name/#:	
Chem.Type/Ther.Class:	5S

PHARMACOL. CATEGORY/INDICATION: Daily multi-vitamin maintenance supplement for adults and children (aged 11 and older) receiving parenteral nutrition.

DOSAGE FORM:	Injection
STRENGTHS:	See Chemist's Review Notes
ROUTE OF ADMINISTRATION:	Intravenous
Rx/OTC:	**_X_ Rx __ OTC**

SUPPORTING DOCUMENTS: Letters of Authorization, allowing reference to the following DMF's: [redacted]

RELATED DOCUMENTS (if applicable): Official minutes (meeting between [redacted] and the FDA, dated 8-20-98), and the following Drug Master Files:

Type/Number	Subject	Holder	Status	Review Date
DMF [redacted]	[redacted]	[redacted]	Adequate	10-21-99
DMF [redacted]	[redacted]	[redacted]	Adequate	12-16-98

CONSULTS: Microbiology .

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Ascorbic Acid (Vitamin C), Retinyl palmitate (Vitamin A), Cholecalciferol (Vitamin D_3), Thiamine (Vitamin B_1), Riboflavin phosphate (Vitamin B_2) Niacinamide, Pyridoxine hydrochloride (Vitamin B_6), Dexpanthenol (Vitamin B_5), *dl*-α-tocopheryl acetate (Vitamin E), Folic acid, Biotin, and Cyanocobalamin (Vitamin B_{12}). The structures, empirical formulae, and molecular weights are provided in this review in the Chemist's Review Notes.

REMARKS: Chemistry Review Number 2 covers the responses to an Information Request (IR) Letter, which was communicated to the firm on March 28th, 2000 (Received be Sabex on 3-31-00). There were five specific information requests outlined in the IR letter; the responses are reviewed in the Chemist's Review Notes. Three of the information requests concerned aluminum testing, as outlined in FR 65(17), pp. 4003-4111 (1-26-00), and are addressed though a commitment to develop, validate, and implement this testing. This is acceptable, since the date of implementation for the aluminum labeling regulation (FR 65, Vol. 17, pp. 4003-4111) is January 26th, 2001. The last two information requests concerned typographical errors in the stability commitment (post-approval); these have been revised acceptably. The responses were provided by FAX transmission and a formal submission will follow.

CONCLUSIONS & RECOMMENDATIONS: Adequate information has been provided, regarding chemistry, manufacturing and controls. The application is approvable from the standpoint of chemistry, pending a satisfactory microbiology consult and an acceptable cGMP status (acceptable EER from the Office of Compliance).

cc:
Org. NDA 21-163 Review # 2
HFD-510
HFD-510/D Lewis/
HFD-510/S. McCort
HFD-102/
R/D Init by: /S/

/S/
David B. Lewis, Ph.D.
Review Chemist

Filename: NDA 21-163 Review # 2.doc

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-163

DATE REVIEWED: 4-07-00

REVIEW #: 1

REVIEWER: David B. Lewis, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	07-19-99	07-20-99	07-29-99
AMENDMENT	12-06-99		
AMENDMENT	01-12-00		

NAME & ADDRESS OF APPLICANT:

SABEX Pharmaceutical Products (Produits Pharmaceutiques)
145 Jules-Leger, Boucherville, PQ, CANADA J4B 7K8
Phone: (450)-641-4903
FAX: (514) 596-1460
Ms. Leonor Ferreira, M.Sc., MBA

Authorized U.S. Agent:

Ken Muhvich, Ph.D.
1818 Circle Road
Ruxton, MD 21204

DRUG PRODUCT NAME

Proprietary:	Multi-12®
Established:	Multiple Vitamins for infusion
Code Name/#:	
Chem.Type/Ther.Class:	5S

PHARMACOL. CATEGORY/INDICATION: Daily multi-vitamin maintenance supplement for adults and children (aged 11 and older) receiving parenteral nutrition.

DOSAGE FORM:	Injection (5 mL solution, Vials 1 and 2)
STRENGTHS:	See Chemist's Review Notes
ROUTE OF ADMINISTRATION:	Intravenous
Rx/OTC:	X Rx __ OTC

SUPPORTING DOCUMENTS: Letters of Authorization, allowing reference to the following DMF's: [redacted]

RELATED DOCUMENTS (if applicable): Official minutes (meeting between [redacted] and the FDA, dated 8-20-98). and the following Drug Master Files:

Type/Number	Subject	Holder	Status	Review Date
[redacted]	[redacted]	[redacted]	Adequate	10-21-99
[redacted]	[redacted]	[redacted]	Adequate	12-16-98

CONSULTS: Microbiology and Office of Post-Marketing Risk Assessment (OPDRA)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Ascorbic Acid (Vitamin C), Retinyl palmitate (Vitamin A), Cholecalciferol (Vitamin D_3), Thiamine (Vitamin B_1), Riboflavin phosphate (Vitamin B_2) Niacinamide, Pyridoxine hydrochloride (Vitamin B_6), Dexpanthenol (Vitamin B_5). *dl*-α-tocopheryl acetate (Vitamin E), Folic acid, Biotin, and Cyanocobalamin (Vitamin B_{12}). The structures, empirical formulae, and molecular weights are provided in this review in the Chemist's Review Notes.

REMARKS: NDA 21-163 concerns Multi-12®, which is a multiple vitamin preparation for infusion, and is formulated with the same active ingredient (vitamin) composition as MVI-12® (AstraZeneca, NDA 8-809). Multi-12® is a sterile product [redacted] consisting of two (2) 5-mL vials, labeled as Vial 1 (nine vitamins), and Vial 2 (three vitamins). Multi-12® is formulated, such, that when the two vials are mixed; the drug product provides a combination of twelve (12) essential oil- and water-soluble vitamins in an aqueous solution. The amounts of each active (vitamin) ingredient are identical between Multi-12® (Sabex) and MVI-12® (AstraZeneca), but the inactive ingredient composition is different between the two drug products. Multi-12® has been (and is presently) marketed in Canada. Ten (10) out of the twelve (12) active ingredients (bulk vitamins) are supplied (and manufactured) by [redacted] (and subsidiaries of), which does not maintain Drug Master Files. The CMC information for the bulk vitamins, which are supplied by [redacted], was provided directly to the NDA in the documents dated 8-26-99 and 10-01-99. *The content of this CMC information package corresponds to that, which was agreed upon in the meeting between [redacted] and the FDA, dated 8-20-98.* The eleventh bulk vitamin, niacinamide, is supplied by [redacted]. no longer maintains an active DMF for this material, and supplied CMC information *via* similar documents dated 1-10-00 and 1-28-00. The other vitamin substance, cyanocobalamin, is supplied by [redacted], along with a letter of authorization, allowing reference to DMF [redacted] The amendment dated 12-06-99 contains updated stability data (long-term and accelerated) for the drug product. The amendment dated 1-12-00 provides Sabex estimates/calculations of the amounts of drug product and vitamin standards for Methods Validation Testing. The analytical methods for the drug product (vitamin assays) need to be validated by the FDA Field Testing laboratory. A Methods Validation (MV) package has been submitted to the appropriate Field Testing Laboratory; the results are pending. Issues of sterility assurance are addressed in the Microbiology Review; results are pending. C. Vincent, reviewer). The amendment dated 4-11-00 contains responses to the Information Request (IR) Letter sent to Sabex on 3-27-00 and received 3-31-00. These responses are addressed in Chemistry Review # 2.

CONCLUSIONS & RECOMMENDATIONS: Information, regarding chemistry, manufacturing and controls is adequate for NDA 21-163. The application is approvable, pending acceptable microbiology review, acceptable cGMP status (acceptable EER), and acceptable response(s) to the Information Request Letter dated 3-27-00.

cc:
Org. NDA 21-163 Review
HFD-510
HFD-510 D Lewis'
HFD-510 S. McCort
HFD-102'
R D Init by: /S/

/S/
David B. Lewis, Ph.D.
Review Chemist

Filename: NDA 21-163 Review.doc

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 5, 2000

FROM: Steve McCort

SUBJECT: EA/Fonsi -Categorical Exclusion

TO: File for NDA 21-163

Per Chemistry Review #1 (See attached page 37 from Dr. David Lewis's Review) Multi-12 (Multiple Vitamins for Infusion)) qualifies for a categorical exclusion pursuant to 21 CFR 25.31(b) and (c).

/S/

Stephen McCort
Project Manger, HFD-510