

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-265**

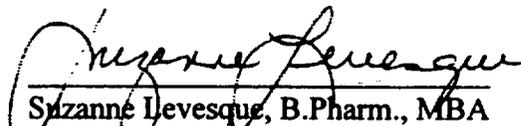
**ADMINISTRATIVE DOCUMENTS**

**SABEX®**Pharmaceutical Products  
Produits pharmaceutiques**PATENT CERTIFICATION**

In accordance with the Federal Food, Drug and Cosmetic Act, as amended September 24<sup>th</sup>, 1984, Patent Certification is hereby provided for our New Drug Application for **Multi-12®/K, Pediatric**, submitted pursuant to section 505(b)(2).

In the opinion and to the best knowledge of SABEX INC., there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug.

SABEX INC.

  
Suzanne Levesque, B.Pharm., MBA  
Vice-President2000-04-10  
Date

Quality Assurance and Regulatory Affairs

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**SABEX INC**145 Jules-Léger  
Boucherville, QC, Canada  
J4B 7K8Tel : 450-641-4903  
Fax : 514-596-1460

EXCLUSIVITY SUMMARY for NDA # 21-265  
Trade Name Inovite *Infuvite Pediatric (multiple vitamins for infusion)* Generic Name \_\_\_\_\_  
for Injection \_\_\_\_\_  
Applicant Name Sabex Inc.  
HFD-510  
Approval Date \_\_\_\_\_

*Since PM took this out maybe we should cover completely your call*

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES / x / NO / \_\_\_ /
- b) Is it an effectiveness supplement? YES / \_\_\_ / NO / x /

If yes, what type (SE1, SE2, etc.)? \_\_\_\_\_

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / \_\_\_ / NO / x /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /\_x\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /\_x\_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_x\_/ NO /\_\_\_/

If yes, NDA # 18-520 Drug Name mvt Pediatric

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_\_\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / \_\_\_ / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / \_\_\_ / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/      NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

\_\_\_\_\_  
\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/      NO /\_\_\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/      NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # \_\_\_\_\_

Investigation #2, Study # \_\_\_\_\_

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO /\_\_\_/

Investigation #2 YES /\_\_\_/ NO /\_\_\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #\_\_, Study # \_\_\_\_\_

Investigation #\_\_, Study # \_\_\_\_\_

Investigation #\_\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
! \_\_\_\_\_  
! \_\_\_\_\_  
!

Investigation #2  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
! \_\_\_\_\_  
! \_\_\_\_\_  
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
! \_\_\_\_\_  
! \_\_\_\_\_  
!

Investigation #2  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
! \_\_\_\_\_  
! \_\_\_\_\_  
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /    /            NO /    /

If yes, explain: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

  / S /    
Signature of Preparer  
Title:   P2022-01-01-01  

  2-21-01    
Date

  / S /    
Signature of Office of ) Division Director

  2-21-01    
Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

cc: Archival NDA/PLA/PMA # \_\_\_\_\_  
HF \_\_\_\_\_/Div File  
NDA/PLA Action Package  
HFD-104/Peds/T.Crescenzi

(revised 3/6/00)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, TERRIE CRESCENZI, HFD-104 (CRESCENZIT)**

**PEDIATRIC PAGE**

(Complete for all original applications and all efficacy supplements)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.**

NDA/PLA/PMA # 21-265 Supplement # \_\_\_\_\_ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

D-510 Trade and generic names/dosage form: Inoovite (Multivitamins for Injection)  
Action: AP

Applicant Sabex, Inc. Therapeutic Class 5S

Indication(s) previously approved Provides for multivitamin maintenance in infants and children up to 11 years of age receiving parenteral nutrition.

Pediatric information in labeling of approved indication(s) is adequate

Proposed indication in this application \_\_\_\_\_

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? \_\_\_ Yes (Continue with questions) \_\_\_ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month)  Infants (1month-2yrs)  Children (2-12yrs)  Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing,

(2) Protocols were submitted and approved.

(3) Protocols were submitted and are under review.

(4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? \_\_\_ Yes \_\_\_ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical review Medical Officer Dr. Jean Temeck (e.g., medical review, medical officer, team leader).

**ISI**

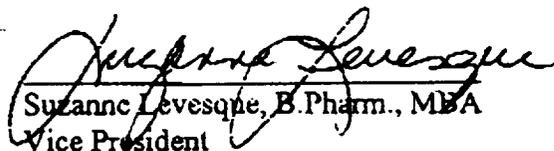
209-01

Steve Mcort, Project Manager

**DEBARMENT CERTIFICATION**

SABEX INC. hereby certifies that it has not and will not use in any capacity the services of any person debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act, in connection with this application.

SABEX INC.

  
Suzanne Levesque, B.Pharm., MBA  
Vice President

2001/02/21  
Date

Quality Assurance & Regulatory Affairs



**SABEX**

# MESSAGE CONFIRMATION

02/20/01 16:46  
ID=FDA CDER DMEDP

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
02/20	00'43"	5145961460	CALLING	02	OK 0000

02/20/01 16:45 FDA CDER DMEDP → 915145961460 NO.194 001



Food and Drug Administration  
Division of Metabolic and Endocrine  
Drug Products, HFD-510  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

## FACSIMILE TRANSMITTAL SHEET

DATE: 2-20-2001

To: LEONAR PERRIERA	From: STAVO MCGONIG
Company: <del>520-896-1140</del>	Division of Metabolic and Endocrine Drug Products
Fax number: <del>520-896-1140</del>	Fax number: (301) 443-9282
Phone number: <del>520-896-1140</del>	Phone number:

Subject: Permanent certification

Total no. of pages including cover:

Comments:

*Stavo McGonig*

**MEMORANDUM OF MEETING MINUTES**  
**DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS**

**Meeting Date:** February 2, 2000

**Time:** 1:30 pm

**Location:** Pkln. 3rd Flr. Potomac Rm.

**Firm:** Sabex

**Drug:** Multivitamin Pediatric IV

**Type of Meeting:** Pre-NDA

**Meeting Chair:** John K. Jenkins, M.D. --  
Acting Division Director, HFD-510

**Meeting Recorder:** Steve McCort  
Project Manager. HFD-510

**FDA Attendees:**

John Jenkins, M.D., Acting Division Director  
David Orloff, M.D., Deputy Director  
Jean Temeck, M.D., Medical Reviewer  
Duu-Gong Wu, Ph.D., Chemistry Team Leader  
David Lewis, Ph.D., Chemistry Reviewer  
David Read, Acting Director, Regulatory Policy Staff  
Hae Young Ahn, Ph.D, Biopharmaceutics Team Leader  
Mary Catchings, Regulatory Counsel  
Sue Yang, Regulatory Project Manager  
Steve McCort, Regulatory Project Manager

**Sabex Inc. Attendees:**

Leonor Ferreira, Director, Regulatory Affairs  
Suzanne Levesque, Vice President, Quality Assurance and Regulatory Affairs  
Michel Riverin, Vice President, Research and Development

**Background:**

The firm in a letter dated December 22, 1999, requested a pre-NDA meeting with the Agency regarding a proposed new drug application for a Pediatric Multivitamin IV preparation. The firm currently has a pending NDA 21-163, for an adult Multivitamin IV preparation under review by the Agency. The Sponsor intends to file a 505(b)(2) application citing the Astra MVI Pediatric NDA 18-920. Since Astra's product is conditionally approved and had not gained full approval,

Sabex has asked the Agency to guide them on the submission approach for their Pediatric Multivitamin IV product. In addition the Firm has specific questions addressed in their meeting package regarding the requirements for submitting their NDA. Prior to the meeting a Federal Register Notice (*FR docket No. 79N-0113 "Pediatric Multivitamin Products: Drug Efficacy Study Implementation; Announcement of Marketing Conditions*) dated January 26, 2000 was published. The notice stated a firm that currently has conditional approval for Pediatric Multivitamins IV can gain full approval provided that the firm submits a labeling supplement by March 27, 2000 and addresses the issues in their supplemental application raised in the Federal Register Notice. Sabex was notified of the FR notice and was sent a copy of it before the meeting.

**Meeting Objective:** To address specific Pre-NDA issues as outlined in the December 22, 1999 cover letter for the proposed Pediatric Multivitamin product.

**Discussion:**

The following discussion was based on the questions taken from the December 22, 1999 pre-NDA Package:

**Question 1: Is the product eligible for an application under section 505(b)(2) of the Food Drug and Cosmetic Act?**

**FDA Response:**

Yes. The Firm can reference the January 26, 2000 Federal Register Notice "Pediatric Multivitamin Products: Drug Efficacy Study Implementation; Announcement of Marketing Conditions." Sabex should provide information that supports the efficacy and safety of their product where differences exist between Sabex's product and Astra's currently marketed Multivitamin product in the application. In Sabex's presentation, the differences between the two preparations were noted as follows: Polysorbate 80 and Polysorbate 20 concentrations, Mannitol concentrations, lack of butylated hydroxytoluene and butylated hydroxyanisole in the Sabex product but present in the Astra product. In addition the Sabex product has two vials, 4 mL and 1 mL, for the ingredients while all the ingredients for the Astra product are contained in one 5 mL vial.

It was pointed out to Sabex that the Federal Register notice allowed Astra (or any other firm) to submit a supplement to the NDA that would allow a firm that has conditional approval to gain full approval provided that they submit this supplement to the Agency by March 27, 2000. Once the supplement is approved, Sabex would have the alternative of submitting a 505(j) application to OGD.

**Question 2: Is the proposed formulation acceptable?**

**FDA Response:**

The formulation appears to be acceptable. However, the dosing requirements of the product in Canada differ from that of similar products in the US. The lack of preservatives in the Sabex product may be an issue in the NDA review.

**Question 3: How much of the pending NDA 21-163 MULTI-12 [adult prep] can be cited in the proposed Multi-12 Pediatric?**

**FDA Response:**

Regarding the CMC data for the drug substance, the same data can be referenced regarding the vitamins, etc. However, stability studies will have to be done for the new product. The method by which Vitamin K is assayed needs to be validated for this application. Regarding microbiology data the Firm should consult with the Microbiology staff at FDA (Peter Cooney, Microbiology Supervisor). For the Clinical section of the NDA the Firm must submit specific literature that supports use in the pediatric population. This should also include specific references that address the safety of the excipients in the proposed product.

**Question 4: Are User Fees Applicable?**

**FDA Response:**

The firm is exempt from paying user fees. However, the firm should still consult with Mike Jones of the User Fee Staff at FDA.

**Other Questions (From Package):**

**1. Can the requirements under the following sections be waived? (See question 1 of package)**

**FDA Response:**

The requirement for clinical studies is not waived. It can be met by submission of the appropriate literature supporting safety and efficacy in the proposed pediatric population. The Firm can submit a waiver for the bioavailability requirement.

**2. For pharmacology and toxicology data can the firm reference the data provided for in NDA 21-163 and provide additional information for the vitamin K?**

**FDA Response:**

Yes.

**3. Can we obtain expedited review for our NDA?**

**FDA Response:**

To obtain a Priority review the firm must provide a medical rationale for why the product will need such review. A shortage of available Pediatric Multivitamin product may justify a Priority review. The firm should consult with Mike Verdi, Office of Compliance, FDA for an update on this situation before applying for an "Expedited Review" for this application.

**Decisions (agreements) reached:**

1. The MULTI-12 Pediatric IV formulation can be submitted as a 505(b)(2) application citing the January 26, 2000 Federal Register Notice (FR docket No. 79N-0113 "Pediatric Multivitamin Products: Drug Efficacy Study Implementation; Announcement of Marketing Conditions."). Once Astra's supplement for NDA 18-820 is approved Sabex could submit a 505(j) application to OGD.
2. The formulation for MULTI-12 is acceptable. However the Firm will have to submit data or literature that supports the safety and efficacy of the proposed product for those differences in the excipients from the currently marketed Astra MVI PEDIATRIC product.
3. No User Fees apply. However the Firm should consult with Mike Jones of the User Fee group at FDA before submission of their NDA.
4. A Priority review can be requested provided that the Firm submits a medical rationale justifying the review. The Firm was also advised to consult Mike Verdi, Office of Compliance, FDA on the status of the Pediatric Multivitamin shortage, since a shortage could provide a medical rationale for a Priority review.
5. The Sponsor may request a waiver of the required pharmacokinetic and bioavailability studies.

**Action Items:**

	<b><u>Item</u></b>	<b><u>Responsible Person</u></b>	<b><u>Due Date</u></b>
1.	The Sponsor will submit their NDA based upon information given to them at the meeting with FDA.	Leonor Ferreira, Sabex	March, 2000

**Action Items:**

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
1. The Sponsor will submit their NDA based upon information given to them at the meeting with FDA.	Leonor Ferreira, Sabex	March, 2000

Minutes Preparer: /S/ 3-15-00  
Chair Concurrence: /S/ 3-16-00

Attachments/Handouts: December 22, 1999 meeting package, January 26, 2000; Federal Register Notice "Pediatric Multivitamin Products; Drug Efficacy Study Implementation; Announcement of Marketing Conditions."

Concurrence: D Lewis 3-1-00/R Steigerwalt 3-1-00/H Ahn 3-2-00/J Temeck 3-2-00  
D Orloff 3-2-00/D Read 3-7-00/M Catchings 3-7-00 / J Jonking 3-16-00

cc: HFD-510/SubjectFile/TVVitamins-2000/Sabex  
HFD-510/Meeting Minutes files  
HFD-510/PM/SMcCort  
HFD-510/JJenkins/DOrloff/JTemeck/RSteigerwalt/SYang  
HFD-870/HAhn  
HFD-820/DWu/DLewis  
HFD-002/DRead/MCatchings

Drafted by: Steve McCort March 1, 2000  
Revised by: Steve McCort March 7, 2000  
Final by: Steve McCort March 13, 2000

MEETING MINUTES

**Division of Metabolic And Endocrine Drug Products, HFD-510**

**Label Review of DRAFT LABELING**

**Application Number:** NDA 21-265

**Name of Drug:** Multi-12<sup>®</sup>-12/K<sub>1</sub> (Multiple Vitamins for Infusion)

**Sponsor:** Sabex Inc.

**Material Reviewed**

**Submission Date(s):** April 20, 2000

**Receipt Date(s):** April 20, 2000

**Background and Summary Description:** The Multi-12/K<sub>1</sub> Pediatric provides for multivitamin maintenance in infants and in children up to 11 years of age receiving parenteral nutrition. The active ingredients are quantitatively and qualitatively identical to that of MVI Pediatric (Astra's product NDA 18-920) which was fully approved. This application was submitted as a 505(b)(2) application. The Multi-12/K<sub>1</sub> labeling was compared with Astra.'s MVI™ Pediatric labeling for this application.

**Review**

The draft labeling dated April 20, 2000, reviewed by the Division of Metabolic and Endocrine Drug Products staff. The following are the labeling comments/recommendations to be conveyed to the Firm:

**MEDICAL:**

**In Dr. Jean Temeck's January 10, 2001, review of the labeling the following changes are recommended:**

The package insert (PI) for MVI-12/K<sub>1</sub> Pediatric should be revised as follows to conform to that for MVI Pediatric given the similar composition of the two products:

**DESCRIPTION:**

- a. The specific amounts of the inactive ingredients in vials 1 and 2 should be specified.
- b. After the contents of vial 2, add:
  - Vitamin A 2,300 IU equals 0.7 mg
  - Vitamin D 400 IU equals 10 mcg
  - Vitamin E 7 IU equals 7 mg
- c. Delete the word "Aqueous" which precedes "multiple vitamin preparation for intravenous infusion" and capitalize the "m" in "multiple".

## INDICATIONS AND USAGE:

Add the following sentence to the end of the fifth paragraph: "Blood vitamin concentrations should be periodically monitored to ensure maintenance of adequate levels, particularly in patients receiving parenteral multivitamins as their sole source of vitamins for long periods of time."

## PRECAUTIONS:

Under "General", delete the first sentence which begins with: "Unlike the adult formulation..."

Revise the second sentence of the first paragraph to read: "In such patients, vitamin K may antagonize the hypoprothrombinemic response to anticoagulant drugs. Add "/INR response" after "prothrombin time" in the third sentence.

Unbold paragraphs 2 and 3 which respectively begin with: "Adequate blood levels..." and "Studies have shown..."

Add the word "may" before "require" in the fourth paragraph.

Add the following after the fourth paragraph:

"In patients receiving parenteral multivitamins, blood vitamin concentrations should be periodically monitored to determine if vitamin deficiencies or excesses are developing.

Polysorbates have been associated with the E-Ferol syndrome (thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis) in low birth weight infants.

Multi-12/K<sub>1</sub> Pediatric should be aseptically transferred to the infusion fluid."

Replace the *Drug interactions* section with:

### **Drug-Drug Interactions**

#### *Physical Incompatibilities*

Multi-12/K<sub>1</sub> Pediatric is not physically compatible with alkaline solutions or moderately alkaline drugs such as Acetazolamide, Chlorothiazide sodium, Aminophylline or sodium bicarbonate. Multi-12/K<sub>1</sub> Pediatric is not physically compatible with ampicillin and it may not be physically compatible with tetracycline HCl. It has also been reported that folic acid is unstable in the presence of calcium salts such as calcium gluconate. Direct addition of Multi-12/K<sub>1</sub> Pediatric to intravenous fat emulsions is not recommended. Consult appropriate references for listings of physical compatibility of solutions and drugs with the vitamin infusion. In such circumstances, admixture or Y-site administration with vitamin solutions should be avoided.

Some of the vitamins in Multi-12/K<sub>1</sub> Pediatric may react with vitamin K bisulfite or sodium bisulfite; if bisulfite solutions are necessary, patients should be monitored for vitamin A, thiamine and ascorbic acid deficiencies."

### **Clinical Interactions**

A number of interactions between vitamins and drugs have been reported which may affect the metabolism of either agent. The following are examples of these types of interactions.

Folic acid may lower the serum concentration of phenytoin resulting in increased seizure frequency. Conversely, phenytoin may decrease serum folic acid concentrations and, therefore, should be avoided in pregnancy. Folic acid may decrease the patient's response to methotrexate therapy.

Pyridoxine may decrease the efficacy of levodopa by increasing its metabolism. Concomitant administration of hydralazine or isoniazid may increase pyridoxine requirements.

In patients with pernicious anemia, the hematological response to vitamin B<sub>12</sub> therapy may be inhibited by concomitant administration of chloramphenicol.

Several vitamins have been reported to decrease the activity of certain antibiotics. Thiamine, riboflavin, pyridoxine, niacinamide, and ascorbic acid have been reported to decrease the antibiotic activity of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated in vitro by ascorbic acid and riboflavin.

Vitamin K may antagonize the hypoprothrombinemic effect of oral anticoagulants

Consult appropriate references for additional specific vitamin-drug interactions.

Add the following section after **Drug-Drug Interactions**:

#### **Drug-Laboratory Test Interactions**

Ascorbic acid in the urine may cause false negative urine glucose determinations.

#### **Carcinogenesis, Mutagenesis, and Impairment of Fertility:**

Add: "and mutagenicity and fertility" after the word: "Carcinogenicity".

### **WARNINGS:**

Revise the first sentence to read: "Multi-12/K<sub>1</sub> Pediatric is administered in intravenous solutions which may contain aluminum that may be toxic."

## ADVERSE REACTIONS:

Revise the first sentence to read: "There have been rare reports of anaphylactic reactions following parenteral multivitamin administration."

Follow this first sentence with: "Rare reports of anaphylactoid reactions have also been reported after large intravenous doses of thiamine."

The adverse reactions after "Allergic" should read: urticaria, shortness of breath, wheezing and angioedema.

## OVERDOSAGE:

Replace the second and third sentences with: "Clinical manifestations of hypervitaminosis A have been reported in patients with renal failure receiving 1.5 mg/day retinol. Therefore, vitamin A supplementation of renal failure patients should be undertaken with caution."

## DOSAGE AND ADMINISTRATION:

In the first paragraph, add: "and children" after "infants".

Revise the beginning of the third paragraph to read: "A daily dose of Multi-12/K<sub>1</sub> Pediatric should be added directly to not less than 100 ml..."

Revise the sequence of dosing based on body weight from smallest to largest (i.e. **For administration to infants weighing < 1 kg should be placed first**).

Revise **For administration to infants weighing < 1 kg** as follows:

The daily dose is 30% of the contents of Vial 1 (1.2 ml) and of Vial 2 (0.3 ml). Do not exceed this daily dose. A supplemental vitamin A may be required for low- birth-weight infants.

Revise **For administration to infants weighing  $\geq$  1 kg and < 3 kg** as follows:

The daily dose is 65% of the contents of Vial 1 (2.6 ml) and of Vial 2 (0.65 ml). Do not exceed this daily dose. A supplemental vitamin A may be required for low- birth-weight infants.

Revise **For administration to infants and children weighing  $\geq$  3 kg up to 11 years of age** as follows:

The daily dose is the entire contents of Vial 1 (4 ml) and of Vial 2 (1 ml) unless there is clinical or laboratory evidence for increasing or decreasing the dosage.

## PHARMACOLOGY

In Dr. Ron Steigerwalt's, May 5, 2000 review of the labeling, the labeling as per Sponsor was judged to be adequate and therefore no changes in labeling were recommended.

However in the E-Mail sent by Dr. Karen Davis Bruno, Pharmacology Team Lead on January 11, 2001, the following labeling changes were recommended.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Carcinogenicity, mutagenesis and fertility studies have not been performed.

Writer was inconsistent here they have "mutagenesis" instead of "mutagenicity" oh well

**BIOPHARMACEUTICS:**

Dr. Robert Shore in his January 10, 2001, review recommended that changes that have been made to other similar products to MULT-12/K1 should be altered to reflect those changes.

**CHEMISTRY:**

**A. Proprietary Name**

The proposed proprietary name "Multi to the Office of Post-Marketing Drug Risk As OPDRA reviewed the suitability of the propo: several recommendations for labeling revisions designed to correct errors with the use of this drug product.

*again  
would we  
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mult-12/k1  
+  
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Infuvite?  
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**OPDRA Consult, regarding the suitability of the proprietary name Multi-12®/K1 Pediatric:**

One primary concern raised in the OPDRA Expert Panel Review related to the sponsor's use of the common medical and chemical abbreviation "K" in the proprietary name. A consensus was reached that, in interpreting prescription orders for this product, the modifier "K" could be confused with the need to add potassium or Vitamin K to the infusion. The letter "K" is commonly used as an abbreviation for potassium in clinical settings. This would result in an excessive dose of either vitamin K or potassium. It was also stated that the use of this modifier placed undue emphasis on one ingredient.

Another OPDRA concern related to the sponsor's use of the modifier "12", rather than "13", which represents the actual number of vitamins in the drug product. Thus, the modifier "12" is both inaccurate and misleading.

The chemistry review team (HFD-820) and the Division agreed with the OPDRA opinion, regarding the proposed tradename "Multi-12/K1 Pediatric". The sponsor was asked to submit another tradename for review. **After consultation with the sponsor, the following name was proposed: INFUVITE PEDIATRIC, which was judged acceptable to the Division.**

OPDRA recommended that the word "kit" be associated with the product name. The chemistry team does not agree with this opinion; **the term "kit" need not be added to the product name.**

**B. Established Name**

OPDRA stated that the established name for the drug product "multiple vitamins for infusion" is not officially recognized by the USP, and should be changed to "multiple vitamins injection". OPDRA thought that inclusion of the phrase "for infusion" in the established name was a safety concern, in that the user may assume that the undiluted product is ready for

infusion. **The chemistry team does not agree with this recommendation.** Currently, the following injectable drug products utilize the same established name (see below)

- NDA 20-924: Cernevit™-12 (multivitamins for infusion)
- NDA 21-163: Multi-12® (multiple vitamins for infusion)
- NDA 8-809: M.V.I.-12® (multi-vitamins for infusion)

OPDRA's concern that the product will be used directly for infusion (without dilution) is allayed by the warning "for dilution in intravenous infusions only" which is printed on the package insert, and on the labels. **The established name (multiple vitamins for injection) should stay unchanged.**

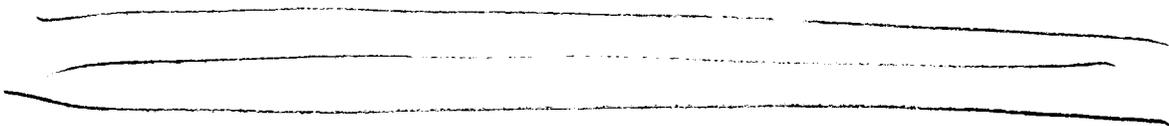
### C. Package Insert

1. \_\_\_\_\_  
\_\_\_\_\_
2. OPDRA recommended that, in the designation of multivitamin content, "mcg" or "microgram" be substituted for the symbol "µg". **The chemistry team agrees with this recommendation.**

### D. Vial and Carton Label

1. OPDRA recommended that the specific contents of Vial 2 be provided on the immediate container (inner) label. The chemistry team does not agree with this opinion. The label for Vial 2 qualifies for the "small label exemption", as defined in 21 CFR 201.10(i)(2). The listing of ingredients may be provided on the carton label, and on the package insert. **The omission of the specific content statement on Vial 2 is acceptable.**
2. OPDRA recommended that the word "CAUTION" be deleted from the "Rx Only" warning. **The chemistry team agrees with this recommendation.**
3. OPDRA recommended that, in the designation of multivitamin content, "mcg" or "microgram" be substituted for the symbol "µg". **The chemistry team agrees with this recommendation.**
4. OPDRA recommended that the container labels be revised to include the phrases "Vial 1 of 2" and "Vial 2 of 2". **The chemistry team does not think that this is necessary; this additional wording need not be added to the container labels.**
5. OPDRA recommended that additional distinctive features be added to each vial to further differentiate between the two (e.g., color, graphics, or text). The use of color coding has never been endorsed by CDER or ONDC. Furthermore, the difference in size (5 mL for Vial 1 and 1 mL for Vial 2) provides adequate differentiation between the two vials. **The chemistry team does not agree with this recommendation.**
6. The aluminum statement on the immediate container labels for Vials 1 and 2 may be deleted due to size and space restrictions.

7.



**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

**RECOMMENDATION:**

With the concurrence of the reviewing staff for this NDA, the above recommendations should be sent to the Sponsor.

IS/

2-04-01

Stephen McCort, Project Manager

IS/

2/7/01

Jean Temeck, M.D., Medical Reviewer

IS/

2/7/01

David Lewis, Ph.D., Chemistry Reviewer

IS/

2/7/01

Duu-Gong Wu, Ph.D., Chemistry Team Leader

IS/

06-FEB-01

Robert Shore, Pharm d, Biopharmaceutics Reviewer

IS/

2/7/01

Hae Young Ahn, Ph.D., Biopharmaceutics Team Leader

IS/

2-5-01

David Orloff, M.D., Division Director

IS/

2/7/01

Karen Davis-Bruno, Ph.D., Pharmacology Team Leader

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:** December 26, 2000

**DUE DATE:** January 31, 2001

**OPDRA CONSULT #:** 01-0001

**TO:** David Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products  
HFD-510

**THROUGH:** Steve McCort, Project Manager  
HFD-510

**PRODUCT NAME:**  
Multi-12®/K<sub>1</sub> Pediatric  
(multiple vitamins for infusion)

**MANUFACTURER:** Sabex, Incorporated  
Boucherville, Qc, Canada J4B 7K8

**NDA #:** 21-265

**SAFETY EVALUATOR:** Carol Pamer, R.Ph.

**SUMMARY:** In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), OPDRA conducted a review of the proposed proprietary name "Multi-12/K<sub>1</sub> Pediatric" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

**OPDRA RECOMMENDATION:** From a safety perspective, OPDRA does not recommend use of the proprietary name "Multi-12/K<sub>1</sub> Pediatric". We have also made recommendations for labeling revisions to minimize potential errors with the use of this product.

/S/

/S/

\_\_\_\_\_  
Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3242  
Fax: (301) 480-8173

\_\_\_\_\_  
Martin Himmel, M.D.  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

# Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

## PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** January 20, 2001  
**NDA NUMBER:** 21-265  
**NAME OF DRUG:** Multi-12/K<sub>1</sub> Pediatric (multiple vitamins for infusion)  
**NDA HOLDER:** Sabex, Incorporated  
Boucherville, Qc, Canada J4B 7K8

### I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the tradename "Multi-12/K<sub>1</sub> Pediatric". A faxed document was also received by HFD-510 and forwarded to OPDRA in which the sponsor provided the rationale for use of the proposed tradename. This consult also provides an analysis of and response to that document.

Multi-12/K<sub>1</sub> Pediatric is a parenteral multiple vitamin preparation that must be diluted prior to infusion. The product is indicated as a daily multivitamin maintenance supplement for infants and children aged up to 11 years of age who are receiving parenteral nutrition. Multi-12/K<sub>1</sub> Pediatric is also indicated for other conditions in which administration of a vitamin by the intravenous route is required (e.g., surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states). It is supplied as a kit containing two vials that collectively contain 13 vitamins in 5 mL.

The vitamin content of Multi-12/K<sub>1</sub> Pediatric is identical to that of an existing U.S. product, M.V.I Pediatric™ (AstraZeneca).

### II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts<sup>1,2,3</sup> as well as several FDA databases<sup>4</sup> for existing drug names which sound alike or look alike to Multi-12/K<sub>1</sub> Pediatric to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5</sup>. An Expert Panel discussion was conducted to review all findings from the searches. Because the name for the adult formulation "Multi-12" was the subject of a previous OPDRA study and the need existed for an expedited review, no prescription studies were conducted.

## A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Multi-12/K<sub>1</sub> Pediatric. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The *primary concerns* raised were related to the additional modifier "K<sub>1</sub>" in the proposed proprietary name. A consensus was reached that, in interpreting written prescription orders for this product, the modifier could be confused with the need to add potassium or Vitamin K to the infusion. The letter "K" is commonly used as a medical abbreviation for potassium in clinical settings. This would result in an excessive dose of either agent or unnecessary potassium. This modifier was also believed to place undue emphasis on one ingredient.

The reference product *M.V.I.-Pediatric* was considered to have some potential for confusion with *Multi-12/K<sub>1</sub> Pediatric*. However, these two products contain identical quantities of active ingredients. It is also likely that only one product would be stocked by a dispensing pharmacy, with the product selection decision being made at the supply stage.

The potential does exist for Multi-12/K<sub>1</sub> Pediatric to be confused with *Multi-12*. It is possible that a prescriber would abbreviate the trade name by omitting the term "Pediatric" in writing orders. This could result in a physician's order being filled with the adult formulation "Multi-12" and an additional vitamin K 1 mg (for example) or "K" (potassium) 1 meq (for example) added.

It was also noted that the *sponsor's use of the modifier "12"*, rather than 13 which represents the actual number of vitamins in the product, is both inaccurate and misleading.

## B. OPDRA RESPONSE TO SABEX FACSIMILE TRANSMITTED 1/17/01

The facsimile provided to the Division of Metabolic and Endocrine Drug Products addressed the need for the sponsor to distinguish between their two formulations of injectable multivitamins, adult and pediatric. In addition to this need for Sabex to name the pediatric formulation currently under review, a mandatory reformulation of the adult product, Multi-12, has also recently been implemented. This will increase the number of vitamins from 12 to 13, with vitamin K added to the adult product as well. We have the following comments on this document.

1. In this fax, three options for naming the pediatric formulation are outlined. The fax specifies why two of those options are eliminated. Sabex addresses concerns of patient or healthcare provider perception of the other 2 proposed names: Multi-13 Pediatric (negative connotation of "13" in North American culture) and Multi Pediatric (confusing meaning, implies "many children"). However, they do not address issues of safety and potential confusion with existing products, as well as commonly used abbreviations (e.g., K for potassium or additional vitamin K). Use of the number "12" as a modifier, rather than "13", is also inaccurate and misleading as noted in the previous section.
2. An existing product, MVI-12, was noted in the Sabex fax as having been reformulated to contain 13 vitamins. In this case, the sponsor (Astra Zeneca) deleted the modifier "12" from the trade name without adding an additional modifier. A similar pattern is used by this sponsor in naming the pediatric formation, MVI Pediatric. In neither case does Astra Zeneca add "K" as a modifier.

3. Mention is made of the names having been successfully registered as trademarks in the United States. Please note that the US PTO does not consider issues of patient safety, possible health care provider confusion, and medical errors in their review of trademarks, as does FDA.
4. We note in the sponsor's fax that a mandatory reformulation of the adult formulation is in process which includes Vitamin K. A similar naming structure, Multi-12/K<sub>1</sub> Adult, is mentioned as an intended name revision by the sponsor. Please note that this name will be subject to approval by ODPRA and is likely to elicit the same concerns.

### C. SAFETY EVALUATOR RISK ASSESSMENT

The primary concerns raised by OPDRA Expert Panel Review related to the sponsor's use of a common medical and chemical abbreviation, "K", in the proprietary name. A consensus was reached that, in interpreting prescription orders for this product, the modifier could be confused with the need to add potassium or Vitamin K to the infusion. The letter "K" is commonly used as a medical abbreviation for potassium in clinical settings. This would result in an excessive dose of either agent or unnecessary potassium. This modifier was also believed to place undue emphasis on one ingredient.

There were 2 significant sound-alike, look-alike names identified by the Expert Panel with respect to "Multi-12/K<sub>1</sub> Pediatric": MVI Pediatric and Multi-12. The active ingredients of the two Pediatric products are identical and Multi-12/K<sub>1</sub> Pediatric will be considered bioequivalent to MVI Pediatric. A facility would also be likely to stock only one brand of this preparation as well, with the product selection being made at the supply reordering stage. However, confusion with Multi-12 could result in excessive dosing of the vitamins contained in the formulation, as well as possible confusion for the need to add Vitamin K or potassium ("K").

It was also noted that the sponsor's use of the modifier "12", rather than 13 which represents the actual number of vitamins in the product, is both inaccurate and misleading.

*For these reasons, we do not recommend use of the name Multi-12/K<sub>1</sub> Pediatric.*

### **III. LABELING, PACKAGING AND SAFETY RELATED ISSUES**

In the review of the container labels, carton labeling, and draft package insert for Multi-12/K<sub>1</sub> Pediatric, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

#### A. PACKAGING

1. Although it is necessary for reasons of chemical incompatibility among the vitamin components to have two separate vials to complete the 13-vitamin supplementation, based on previous experience with evaluation of medication errors, this type of packaging configuration is error-prone. We suggest the following to provide additional reminders to personnel using the product that each component individually does not comprise a complete dose.
  - a. Add the word "kit" to the product name, e.g. Multi-12/K<sub>1</sub> Pediatric™ Kit.
  - b. Revise the container labels for Vial 1 and Vial 2 to include the phrases "VIAL 1 of 2" and "VIAL 2 of 2".

- c. Provide additional distinctive features for each vial to further differentiate the two vials. Suggested features are (but not limited to) label color, graphics, or text.

**B. CONTAINER LABEL (single-dose packages, Vials 1 and 2)**

1. *The established drug name* chosen by the manufacturer for this product, “multiple vitamins for infusion” is a pharmaceutical dosage form that is not officially recognized by the United States Pharmacopeia in their official compendia.

Including the phrase “for infusion” in the established drug name is also a *safety concern* in that the user may assume that the undiluted product is ready for infusion, the reverse of the likely intent of the manufacturer.

*We suggest that the established name be revised, based upon the USP/NF<sup>6</sup>, to the following:*

**“Multiple Vitamins Injection”.**

2. The specific contents of Vial 2 are not currently provided. This information must be listed on the label.
3. Delete the word “CAUTION” which appears before “Rx Only”.
4. See also comments as stated above.

**C. CARTON LABELING and PACKAGE INSERT LABELING**

1. In the designation of multivitamin content, *we recommend substitution of “mcg” or “micrograms” for the symbol “μg”, as the Greek symbol is often mistaken for “mg”, resulting in a 1000-fold overdose.*
2. See also comments as stated above.

**APPEARS THIS WAY  
ON ORIGINAL**

#### IV. RECOMMENDATIONS

1. From a safety perspective, OPDRA does not recommend use of the proprietary name Multi-12/K<sub>1</sub> Pediatric.
2. We recommend that the term "Kit" be associated with the product name (see "PACKAGING" above).
3. We have made recommendations for labeling revisions to minimize errors with the use of this product.
4. The established name of this product needs to be revised to comply with USP/NF standards. The Labeling and Nomenclature Committee (LNC) should be consulted regarding this issue.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3199.

151

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Carol Pamer, R.Ph.  
Safety Evaluator  
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

151

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Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-265  
HFD-510; Division Files/Steve McCort, Project Manager  
HFD-510; David Orloff, Acting Division Director  
HFD-440; Mary Dempsey, Project Manager, OPDRA  
HFD-400; Carol Pamer, Safety Evaluator, OPDRA  
HFD-400; Peter Honig, Director, OPDRA  
HFD-400; Jerry Phillips, Associate Director, OPDRA

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<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

<sup>2</sup> American Drug index, 42<sup>nd</sup> Edition, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>4</sup> Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-99, and the electronic online version of the FDA Orange Book.

<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>6</sup> USP 24/NF 19: U.S. Pharmacopeia and National Formulary, 1999, The United States Pharmacopeial Convention, Inc., Rockville, MD, p.2112, "Injections".

See Medical Review.

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 21265/000  
Stamp: 21-APR-2000 Regulatory Due: 21-FEB-2001  
Applicant: SABEX  
J4B 7K8  
BOUCHERVILLE, QUEBEC, CA

Priority: 5S  
Action Goal:  
Brand Name: MULTI-12/K1 PEDIATRIC(MULTIPLE VITAMINS/  
Established Name:  
Generic Name: MULTI-12/K1 PEDIATRIC(MULTIPLE VITAMINS/  
Dosage Form: INJ (INJECTION)  
Strength: N/A

Org Code: 510  
District Goal: 23-DEC-2000

FDA Contacts: S. MCCORT (HFD-510) 301-827-6415 , Project Manager  
D. LEWIS (HFD-510) 301-827-6420 , Review Chemist  
D. WU (HFD-510) 301-827-6375 , Team Leader

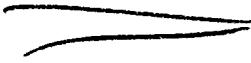
Overall Recommendation:

ACCEPTABLE on 24-NOV-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment: 

DMF No:  
AADA No:

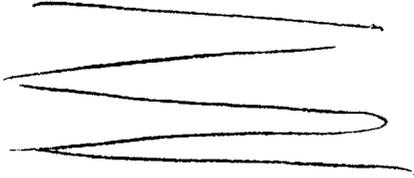
Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 24-NOV-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: 

Establishment: 

DMF No:  
AADA No:

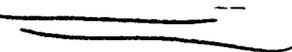
Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 12-JUN-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: 

Establishment: SABEX  
145 JULES-LEGER STREET  
BOUCHERVILLE, QC, , CA j4b 7k8

DMF No:  
AADA No:

Profile: SVS OAI Status: NONE  
Last Milestone: OC RECOMMENDATION

Responsibilities: 

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Milestone Date: 12-JUN-2000  
Decision: ACCEPTABLE  
Reason: BASED ON FILE REVIEW

Establishment: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

DMF No:  
AADA No:

Profile: CTL            OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 10-JUL-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

**M E M O R A N D U M****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** February 5<sup>th</sup>, 2001

**FROM:** David Lewis, Ph.D., review chemist, DNDCII, ONDC

**SUBJECT:** OPDRA (informal) second consult, regarding NDA 21-265

**TO:** NDA 21-265 Division File

The original NDA 21-265 (Sabex, Inc.) proposed the tradename Multi-12/K1 Pediatric for the drug product. The labeling was forwarded to OPDRA for consult. OPDRA opined that this tradename was unacceptable for the drug product, and DMEDP agreed with this position. The firm was asked to submit an alternate tradename for the drug product. On February 2<sup>nd</sup>, Sabex proposed the proprietary name "Infuvite Pediatric" for the drug product. OPDRA was consulted via Telephone, regarding this tradename. They objected to its use, because they considered "Infuvite" to be misleading, based on a potential sound-alike/look-alike product name Folvite®, which is an injectable folic acid drug product. DMEDP did not agree with this assessment and decided to accept the alternate tradename "Infuvite Pediatric" for the drug product.

**Conclusion: The proposed tradename "Infuvite Pediatric" is acceptable for use with the drug product.**

**M E M O R A N D U M**

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

**DATE:** January 30<sup>th</sup>, 2001

**FROM:** David Lewis, Ph.D.

**SUBJECT:** OPDRA Consult, regarding NDA 21-265

**TO:** NDA 21-265 Division File

The OPDRA consult contained the following observations, comments, and recommendations, regarding NDA 21-265 [proposed name: Multi-12®/K<sub>1</sub> Pediatric (Multiple Vitamins for Infusion)], which was filed by Sabex, Inc. (Boucherville, PQ, CANADA) on April 20<sup>th</sup>, 2000.

- **OPDRA:** The established name "multiple vitamins for infusion" is a pharmaceutical dosage form that is not officially recognized by the USP. Including the phrase "for infusion" in the established drug name is also a safety concern in that the user may assume that the undiluted product is ready for infusion.

History: Other Non-proprietary names:

1. NDA 20-924: Cernevit™-12 (multivitamins for infusion) For dilution in infusions only
2. NDA 21-163: Multi-12® (multiple vitamins for infusion) For intravenous infusion after dilution only
3. NDA 8-809: M.V.I.®-12 (Multi-vitamin Infusion) For dilution in intravenous infusions only
4. NDA 18-920: M.V.I.® Pediatric (Multi-vitamins for Infusion) For dilution in intravenous infusions only
5. NDA 21-265: Multi-12®/K<sub>1</sub> Pediatric (Multiple Vitamins for Infusion) For dilution in intravenous infusions only

*I do not agree with this particular OPDRA opinion. The non-proprietary name "Multiple Vitamins for Infusion" is acceptable, having been approved for NDA's 20-924, 21-163, and 18-920. The disclaimer "for dilution in intravenous infusions only" is acceptable, being essentially identical to that for the four previously approved (and presently marketed) multiple vitamin injectable drug products. **The established name "multiple vitamins for infusion" is acceptable.***

Conclusion

Overall OPDRA recommendations:

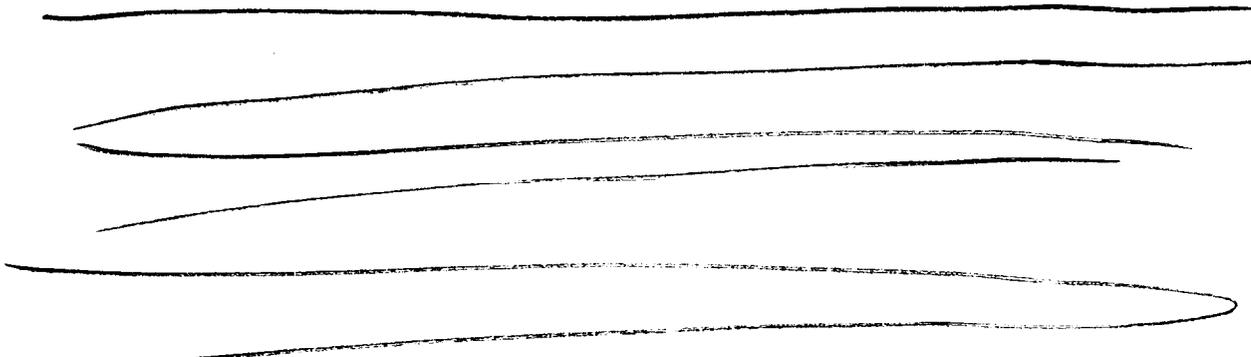
1. From a safety perspective, OPDRA does not recommend the use of the proprietary name Multi-12/K<sub>1</sub> Pediatric. **I agree with this assessment.** If the proprietary name is to be changed, the proprietary name for the adult formulation, Multi-12® should concurrently be changed.
  2. OPDRA recommends that the term "kit" should be associated with the product name. **I do not agree with this recommendation.**
  3. OPDRA has made recommendations for labeling revisions to minimize errors with the use of this product. **Some of these recommendations should be forwarded back to the sponsor; others should not. See individual comments, regarding each specific recommendation.**
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APPEARS THIS WAY  
ON ORIGINAL

1. Change the product names to Multi-13® and Multi-13® Pediatric.
2. Delete the numeral from the name, and go with a different proprietary name (for both Multi-12® and Multi-12®/K<sub>1</sub> Pediatric). The two names could/should be related, such as \_\_\_® and \_\_\_®-Pediatric.

- **OPDRA:** The word "kit" should be added to the product name, e.g., Multi-12®/K<sub>1</sub> Pediatric Kit.

*I do not think that this is necessary. The term "kit" is not used for other 2-vial multiple vitamin injections (M.V.I.®-12 and Multi-12®; NDA's 8-809 and 21-163).*

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- **OPDRA:** Additional distinctive features should be added to each vial to further differentiate between the two (e.g., color, graphics, or text).

*I do not think this is necessary. The use of color-coding has never been endorsed by CDER or by ONDC. The two vials differ in size (5 mL for Vial 1 and 1 mL for Vial 2).*

(b4)

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

<b>RECORD OF TELEPHONE CONVERSATION/MEETING</b>	<b>DATE: 2-02-01</b>
<p>I spoke with Ms. Ferreira, regarding an alternate trade name for the drug product, since the proposed name "Multi-12/K1 Pediatric) was rejected by OPDRA, and by DMEDP. She proposed the tradename "Infuvite Pediatric" for NDA 21-265, and "Infuvite" for the related adult formulation NDA 21-163 (approved tradename Multi-12®).</p>	<b>NDA NUMBER: 21-265</b>
	<b>PRODUCT NAME: Infuvite Pediatric</b>
	<b>FIRM NAME: Sabex, Inc.</b>
	<b>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:</b> Leonor Ferreira, Director Regulatory Affairs
<b>SIGNATURE:</b> <i>/s/</i>	<b>TELEPHONE NUMBER:</b> (450) 641-4903 X2161 (Ph) (450) 596-0003 (FAX)  <b>DIVISION: DMEDP</b>

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME <b>LEONOR FERREIRA</b>	TITLE <b>DIRECTOR, REGULATORY AFFAIRS</b>
FIRM/ORGANIZATION <b>SABEX INC. 145 Jules Leger Street, Boucherville (QC) CANADA</b>	
SIGNATURE 	DATE <b>2001-02-12</b>

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