

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-559**

**ADMINISTRATIVE DOCUMENTS**

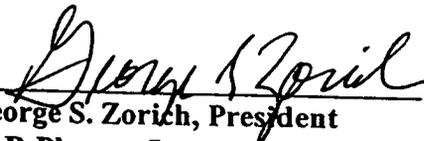
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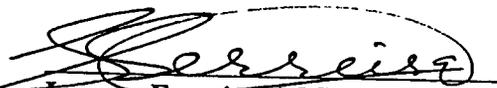
**PATENT CERTIFICATION**

In accordance with the Federal Food, Drug and Cosmetic Act, as amended September 24, 1984, Patent Certification is hereby provided for our New Drug Application for *INFUVITE Adult* submitted pursuant to section 505 (b)(2).

In the opinion and to the best knowledge of Sabex 2002 Inc., there are no patents that claim the listed drug referred to in this application or that claims a use of the listed drug.

  
George S. Zorich, President  
SAB-Pharma Inc.

4/16/03  
Date

  
Leonor Ferreira, M.Sc., MBA  
Director, Regulatory Affairs

04/25/03  
Date

EXCLUSIVITY SUMMARY for NDA # 21-559 SUPPL #

Trade Name INFUVITE ADULT PHARMACY BULK PACKAGE

Generic Name (multiple vitamins for infusion)

Applicant Name Sabex 2002 Inc.

HFD- 510

Approval Date TBD

**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 /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

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 /  /

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?

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 # 21-163 Drug Name Infuvite Adult

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: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

{See appended signature page.}

5/20/2003

\_\_\_\_\_  
Enid Galliers

Title: Chief, Project Management Staff, DMEDP

{See appended signature page.}

David G. Orloff, MD  
Director, DMEDP

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

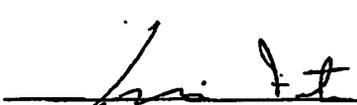
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

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David Orloff  
5/21/03 03:10:37 PM

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

Sabex 2002 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. In addition, Sabex 2002 Inc. states that neither Sabex 2002 Inc. nor any individuals, partnerships, corporations, or associations responsible for the development or submission of this application have been convicted as described in Section 306 (a) and (b) of the Federal Food, Drug and Cosmetic Act.

  
\_\_\_\_\_  
**Louise Fortin, Biochemist  
Manager, Regulatory Affairs**

2003-05-21  
**Date**

**SABEX 2002 INC**  
145 Jules-Léger  
Boucherville, QC, Canada  
J4B 7K8

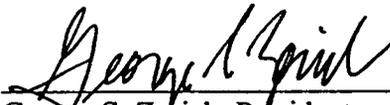
Tel : 450-641-4903  
Fax : 514-596-1460

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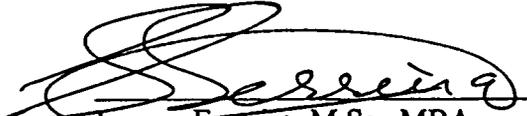
01 008

**DEBARMENT CERTIFICATION**

Sabex 2002 Inc. hereby certifies that, to the best of its knowledge, 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. In addition, to the best of its knowledge, Sabex 2002 Inc. states that neither Sabex 2002 Inc. nor any individuals, partnerships, corporations, or associations responsible for the development or submission of this application have been convicted as described in Section 306 (a) and (b) of the Federal Food, Drug and Cosmetic Act.

  
\_\_\_\_\_  
George S. Zorich, President  
SAB-Pharma Inc.

4/16/03  
Date

  
\_\_\_\_\_  
Leonor Ferreira, M.Sc., MBA  
Director, Regulatory Affairs

04/25/03  
Date

**NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST**

NDA 21-559 / SE \_\_\_\_\_

Drug Infrin Adult PBP Applicant Sabey

RPM Gollies Phone \_\_\_\_\_

505(b)(1)

505(b)(2) Reference listed drug Fed. Reg. Notices

Fast Track

Rolling Review

Review priority:  S  P

Pivotal IND(s) None

Application classifications:

Chem Class 5  
Other (e.g., orphan, OTC) \_\_\_\_\_

PDUFA Goal Dates:

AGD = 5/23/03 Primary 6/16/03  
Secondary \_\_\_\_\_

Arrange package in the following order:

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:  User Fee Paid  
 User Fee Waiver (attach waiver notification letter)  
 User Fee Exemption

*No Fee 505(b)(2)*

- ◆ Action Letter.....  AP  AE  NA

◆ Labeling & Labels

- FDA revised labeling and reviews..... \_\_\_\_\_
- Original proposed labeling (package insert, patient package insert) ..... \_\_\_\_\_
- Other labeling in class (most recent 3) or class labeling..... \_\_\_\_\_
- Has DDMAC reviewed the labeling? .....  Yes (include review)  No
- Immediate container and carton labels ..... \_\_\_\_\_
- Nomenclature review ..... \_\_\_\_\_

- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application  is  is not on the AIP.

Exception for review (Center Director's memo)..... \_\_\_\_\_  
OC Clearance for approval..... \_\_\_\_\_

- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review)
- ◆ Post-marketing Commitments
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- ◆ Was Press Office notified of action (for approval action only)?.....
  - Copy of Press Release or Talk Paper.....
- ◆ Patent
  - Information [505(b)(1)] .....
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- ◆ Exclusivity Summary .....
- ◆ Debarment Statement .....
- ◆ Financial Disclosure
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....
- ◆ Correspondence/Memoranda/Faxes .....
- ◆ Minutes of Meetings .....
- Date of EOP2 Meeting \_\_\_\_\_
- Date of pre NDA Meeting \_\_\_\_\_
- Date of pre-AP Safety Conference \_\_\_\_\_
- ◆ Advisory Committee Meeting .....
- Date of Meeting .....
- Questions considered by the committee .....
- Minutes or 48-hour alert or pertinent section of transcript .....
- ◆ Federal Register Notices, DESI documents .....

No

Materials requested in AP letter

N/A

Yes  No

✓

✓

✓

No

→

**CLINICAL INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....
- ◆ Clinical review(s) and memoranda .....

N/A

- ◆ Safety Update review(s) ..... N/A
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred Pediatric Page..... N/A
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable
- ◆ Statistical review(s) and memoranda ..... N/A
- ◆ Biopharmaceutical review(s) and memoranda..... N/A
- ◆ Abuse Liability review(s) ..... N/A  
 Recommendation for scheduling .....
- ◆ Microbiology (efficacy) review(s) and memoranda ..... N/A
- ◆ DSI Audits ..... N/A
  - Clinical studies  bioequivalence studies .....

**CMC INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda ..... 5.20.03
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ◆ DMF review(s) ..... N/A
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... 5.20.03
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... 01.29.03
- ◆ Facilities Inspection (include EES report)  
 Date completed 07.14/11-2003  Acceptable  Not Acceptable
- ◆ Methods Validation .....  Completed  Not Completed

**PRECLINICAL PHARM/TOX INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda ..... N/A
- ◆ Memo from DSI regarding GLP inspection (if any) .....



- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... N/A

**APPEARS THIS WAY  
ON ORIGINAL**

10 Draft Labeling Page(s) Withheld

2 Page(s) Withheld

,

**DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS**

**PROJECT MANAGER LABELING REVIEW**

**Application Number:** NDA 21-559

**Name of Drug:** Infuvite™ *ADULT* (Multiple Vitamins for Infusion)  
Pharmacy Bulk Package (PBP)

**Applicant:** Sabex 2002 Inc.

**Labeling submissions:** August 14, 2002,  
October 29, 2002  
November 15, 2002  
May 16, 2003  
May 21, 2003

**Material Reviewed:**

**Submissions dated:** May 21, 2002  
**Submissions received:** May 21, 2002 (e-mail)

**Background and Summary**

This application adds a Pharmacy Bulk Package (PBP) to the already approved single dose presentation of Infuvite™ *ADULT* (Multiple Vitamins for Infusion). As required in the draft guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, a new NDA was unbundled from the firm's submission of a supplement that requested the addition to NDA 21-163 (Infuvite Adult) of the pharmacy bulk package presentation to the single-dose, two-vial presentation. Infuvite *ADULT* is a sterile product indicated as a daily, maintenance dose, multivitamin product for total parenteral nutrition (TPN) for adults and children 11 years of age and older. This product was reformulated (SCF-002) to meet the requirements published in Federal Register 65: 21200-21201 (April 20, 2000); it contains 13 vitamins, including vitamin K. Infuvite *ADULT* Pharmacy Bulk Package is supplied as a carton of two 50 mL vials which can prepare 10 doses: 5 mL each of Vial 1 and Vial 2 must be added directly to not less than 500 mL sterile infusion fluid.

A requirement to list aluminum content and specified warning information in the labeling of large and small volume parenteral (LVP and SVP, respectively) drug products was published in Federal Register 65: 4103-4111 (January 26, 2000). The implementing regulation is found at 21 CFR 201.323. Implementation of this labeling requirement has been postponed twice from the

original effective date of January 26, 2001, until the current effective date of January 26, 2004.

**REVIEW:**

This review compared the revised draft labeling dated May 21, 2003, with the approved labeling for NDA 21-163/S-005 and with the changes requested in the May 14, 2003, chemistry DR letter (NDA 21-559) and in a May 20, 2003, telephone call between Louise Fortin of Sabex and this reviewer.

NDA 21-163/S-005 provided for (a) changes to the stability protocol with respect to monitoring aluminum content, (b) changes to aluminum content specifications, and (c) additions to the Vial 1 and Vial 2 labels to list the maximum aluminum content "Contains no more than 475 mcg/L of aluminum (combined Vials 1 and 2)." The firm has not submitted FPL for NDA 21-163/S-005 because they have not printed it yet and will delay implementation until the required January 26, 2004, date.

The final draft labeling (NDA 21-559) does not contain the maximum aluminum content statement. The firm made a commitment (May 16, 2003) to submit a CBE-0 supplement to add the aluminum content information to the labels prior to the required implementation date. The applicant requested this delay because it is waiting to measure aluminum content from a post-expiry date lot and does not yet have the data needed to support the maximum aluminum content statement.

**REVIEWER COMMENT:** This is acceptable.

**The following additional changes are noted:**

**PACKAGE INSERT - PHARMACY BULK PACKAGE**

- The phrase "**PHARMACY BULK PACKAGE**" is inserted in bold, upper case letters between the proprietary name and the established name.
- The boxed phrase "**Pharmacy Bulk Package – Not for Direct Infusion**" is inserted immediately above the **DESCRIPTION** section.
- The first paragraph replaces \_\_\_\_\_ with

**"INFUVITE® ADULT (PHARMACY BULK PACKAGE)** is a sterile product consisting of 2 vials – 1 each of Vial 1 (50 mL) and Vial 2 (50 mL Fill in 100 mL Vial), provided as a pharmacy bulk package.

**"A pharmacy bulk package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous infusion."**

- Wherever \_\_\_\_\_ appears in NDA 21-163/S-005, it is replaced with **INFUVITE® ADULT (PHARMACY BULK PACKAGE)** throughout NDA 21-559.

- In the **DOSAGE AND ADMINISTRATION** section, the paragraph

\_\_\_\_\_

is replaced by

“Preparation of **INFUVITE® ADULT (PHARMACY BULK PACKAGE)** for intravenous feeding should be done by transferring the contents of Vial 1 into the contents of Vial 2 to provide ten 10 mL single doses. One daily 10 mL dose should be added directly to not less than 500 mL, and preferably 1 000 mL, of intravenous dextrose, saline or similar infusion solutions. Discard any unused portion.”

- The following pharmacy bulk package-specific instructions are added to the end of the **DOSAGE AND ADMINISTRATION** section:

Once closure system has been compromised, withdrawal of container contents should be completed within 4 hours.

**INFUVITE® ADULT (PHARMACY BULK PACKAGE)** IS A PHARMACY BULK PACKAGE. IT IS NOT INTENDED FOR DIRECT INFUSION. DISCARD UNUSED PORTION.

**DIRECTIONS FOR DISPENSING FROM PHARMACY BULK VIAL**

The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion. The Pharmacy bulk package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). Dispensing from Pharmacy Bulk Vial should be completed as soon as possible after initial entry.

- The **HOW SUPPLIED** section replaces the NDC numbers and description for the single dose carton and the 5 X single-dose carton with the following:

**INFUVITE® ADULT (PHARMACY BULK PACKAGE)** – NDC 54643 5649 2, is available in boxes containing 2 vials – 1 each of Vial 1 (50 mL) and Vial 2 (50 mL Fill in 100 mL Vial). Mix contents of Vial 1 with Vial 2 to provide 10 single doses.

- The “Store under refrigeration, 2-8 °C (36-46 °F)” statement is moved from before the **HOW SUPPLIED** section to after it.

- The following phrases are added and follow the manufacturer's name at the end of the PI:

Issued: Month/Year

*INFUVITE® is a registered trademark of Sab-Pharma Inc.*

**NOTE:** The final draft labeling (PI) for NDA 21-559 includes the required aluminum warning.

**REVIEWER COMMENT:** The package insert is acceptable.

— VIAL LABELS (IMMEDIATE CONTAINER):

Comparison of the NDA 21-163/S-005 single-dose vial labels to the NDA 21-559 PBP labels-

- **VIAL 1**

**MAIN PANEL**

- The draft label replaces \_\_\_\_\_, with NDC 54643 5649 2, Product Code 56492, and 50 mL, respectively.
- "PHARMACY BULK PACKAGE" is added after "INFUVITE® ADULT."
- The boxed phrase "Pharmacy Bulk Package – Not for Direct Infusion" is inserted immediately after "For intravenous infusion after dilution only"
- \_\_\_\_\_ is deleted.
- "Rx only" is moved to the bottom of the panel.
- "Protect from light" is added – after the storage conditions statement.

**RIGHT PANEL**

- \_\_\_\_\_ is replaced by "Each 5 mL in Vial 1 contains:"
- The phrase \_\_\_\_\_ is omitted. See review comment above.
- The distributor information is moved to the lower part of this panel.

**LEFT PANEL**

- The phrase " \_\_\_\_\_ is replaced by:  
**Transfer the contents of Vial 1 into Vial 2 to provide ten 10 mL single doses. Each 10 mL single dose should be added to not less than 500 mL of infusion fluid.**

Once closure system has been compromised, withdrawal of container contents should be completed within 4 hours.

**DISCARD UNUSED PORTION**

**REVIEWER COMMENT:** The Vial 1 label is acceptable.

• **VIAL 2**

**MAIN PANEL**

- The draft label replaces \_\_\_\_\_ with NDC 54643 5649 2, Product Code 56492, and “50 mL Fill in 100 mL Vial,” respectively.
- “**PHARMACY BULK PACKAGE**” is added after “**INFUVITE® ADULT.**”
- The boxed phrase “**Pharmacy Bulk Package – Not for Direct Infusion**” is inserted immediately after “**For intravenous infusion after dilution only.**”
- “ \_\_\_\_\_ ” is deleted.
- “**Rx only**” is moved to the bottom of the panel.
- “**Protect from light**” is added – after the storage conditions statement.

**RIGHT PANEL**

- “ \_\_\_\_\_ ” is replaced by “**Each 5 mL in Vial 1 contains:**”

**LEFT PANEL**

- The phrase “ \_\_\_\_\_ ” is replaced by:

**Transfer the contents of Vial 1 into Vial 2 to provide ten 10 mL single doses. Each 10 mL single dose should be added to not less than 500 mL of infusion fluid.**

Once closure system has been compromised, withdrawal of container contents should be completed within 4 hours.

**DISCARD UNUSED PORTION**

- The phrase “ \_\_\_\_\_ ” is omitted. See review comment above.

**REVIEWER COMMENT:** The Vial 2 label is acceptable.

**CARTON LABEL**

**TOP FLAP**

- “**PHARMACY BULK PACKAGE**” is added after “**INFUVITE® ADULT.**”

**FRONT PANEL**

- The PBP label replaces \_\_\_\_\_ with NDC 54643 5649 2, and adds Product Code 56492.
- The boxed phrase “**PHARMACY BULK PACKAGE NOT FOR DIRECT INFUSION**” is inserted immediately above “**For intravenous infusion after dilution only.**”

- The following description of the contents

~~\_\_\_\_\_~~

is replaced by:

**Contents: Vial 1 (50 mL) and Vial 2 (50 mL Fill per 100 mL Vial).**

**Both vials combined produce 10 single doses.**

#### **SIDE PANEL**

- The phrase "~~\_\_\_\_\_~~"

is replaced by:

**Transfer the contents of Vial 1 into Vial 2 to provide ten 10 mL single doses. Each 10 mL single dose should be added to not less than 500 mL of infusion fluid.**

Once closure system has been compromised, withdrawal of container contents should be completed within 4 hours.

- The following phrase is added after "Usual dosage: See Package Insert."

**DISCARD UNUSED PORTION**

#### **BACK PANEL**

- "PHARMACY BULK PACKAGE" is added after "INFUVITE<sup>®</sup> ADULT."

**REVIEWER COMMENT:** The carton label is acceptable

#### **RECOMMENDATIONS**

**PACKAGE INSERT, VIAL 1 LABEL, VIAL 2 LABEL, AND CARTON LABELS:**  
**Satisfactory.**

*{See appended electronic signature}*

**Enid Galliers**  
**Chief, Project Management Staff**

Supervisory Comment/Concurrence:

*{See appended electronic signature}*

David Orloff, MD  
Director, DMEDP

— Drafted by E. Galliers/ May 21, 2003

Finalized: E. Galliers/05.22.2003/

Filename: \File Cabinet\Vitamins\21559\21559.pmlblrev.doc

**PM LABELING REVIEW**

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

-----  
Enid Galliers  
5/22/03 06:48:00 PM  
CSO

David Orloff  
5/22/03 07:12:29 PM  
MEDICAL OFFICER

**CONSULTATION RESPONSE**  
Division Of Medication Errors And Technical Support  
Office Of Drug Safety  
(DMETS; HFD-420)

DATE RECEIVED: FEB-13-2003

DUE DATE: MAY-15-2003

ODS CONSULTS:  
03-0063 and 03-0153

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

THROUGH: David Lewis, Ph.D.  
Project Manager, Division of Metabolic and Endocrine Drug Products  
HFD-510

PRODUCT NAME:  
Infuvite Adult  
(Multiple Vitamins for Infusion) Pharmacy Bulk Package  
and

NDA SPONSOR:  
SABEX 2002 INC.

NDA #: 21-559 and

SAFETY EVALUATOR: Marci Lee, PharmD

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names "Infuvite Adult" and " " to determine the potential for confusion with approved proprietary and established names as well as pending names.

**RECOMMENDATIONS:**

1. DMETS does not recommend the use of the word ' ' in the proprietary name, Infuvite Adult
2. \_\_\_\_\_
3. DMETS recommends implementation of the labeling revisions described in Section III.
4. DDMAC \_\_\_\_\_

/S/

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Carol Holquist, RPh  
Deputy Director,  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: 301-827-3242 Fax: 301-443-9664

/S/

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Jerry Phillips, RPh  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420; Parklawn Rm. 6-34  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 5, 2003  
NDA NUMBER: 21-559 and 21-646  
NAME OF DRUG: Infuvite Adult \_\_\_\_\_ and Infuvite Pediatric \_\_\_\_\_  
(Multiple Vitamins for Infusion) Pharmacy Bulk Package  
NDA SPONSOR: SABEX 2002 INC.

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 "Infuvite Adult \_\_\_\_\_" and "Infuvite Pediatric \_\_\_\_\_", regarding potential name confusion with other proprietary or established drug names.

In addition, the Division of Metabolic and Endocrine Drug Products (HFD-510) specifically requested that DMETS consider the labeling related to the *pharmacy bulk package* dispensing instructions.

PRODUCT INFORMATION

The single dose formulation for Infuvite Adult was approved MAY-18-2000. The single dose formulation for Infuvite Pediatric was approved FEB-21-2001. The only difference between the existing Infuvite products and the proposed products is the proposal of the pharmacy bulk package.

Infuvite Adult \_\_\_\_\_ is indicated as a daily multivitamin maintenance dosage for adults and children aged 11 years and older receiving parenteral nutrition. Infuvite Pediatric \_\_\_\_\_ is indicated as a daily multivitamin maintenance dosage for infants and children up to \_\_\_\_\_ age receiving parenteral nutrition. These products are also indicated in other situations where administration of multivitamins by the intravenous route is required. Such situations include surgery, extensive burns, fractures and other trauma, serious infectious diseases, and \_\_\_\_\_ comatose states, which may provoke a "stress" situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. Infuvite Adult \_\_\_\_\_ and Infuvite Pediatric \_\_\_\_\_ (administered in intravenous fluids under proper dilution) contribute to the intake of necessary vitamins toward maintaining the body's normal resistance and repair processes.

Preparation of Infuvite Adult \_\_\_\_\_ for intravenous feeding should be done by transferring the contents of Vial 1 into the contents of Vial 2 to provide ten 10 mL single doses. One daily 10 mL dose should be added directly to not less than 500 mL, and preferably 1,000 mL of intravenous infusion solution. Discard any unused portion.

The daily dose of Infuvite Pediatric \_\_\_\_\_

1. Methodology for Infuvite Adult \_\_\_\_\_ studies

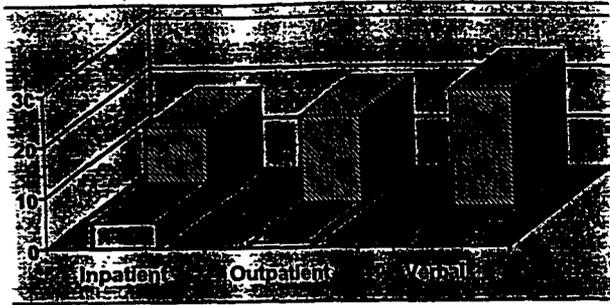
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Infuvite Adult \_\_\_\_\_ with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 105 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote inpatient and outpatient prescriptions for Infuvite Adult \_\_\_\_\_, each consisting of a combination of marketed and unapproved drug products. These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Infuvite Adult _____	
Inpatient:	
<i>Infuvite Adult _____ for use by home nurse</i>	
Outpatient:	Verbal:
<i>Infuvite Adult _____ #1</i>	"... The last prescription is Infuvite Adult _____ Dispense one. For use at home with a home nurse."

2. Results for Infuvite Adult \_\_\_\_\_ studies

Results of these exercises are summarized below:

Study	No. of participants	# of responses	"Infuvite Adult _____ response"	Other response
Written: Inpatient	35	21 (60%)	5 (24%)	16 (76%)
Written Outpatient	31	19 (61%)	1 (5%)	18 (95%)
Verbal:	39	23 (59%)	0 (0%)	23 (100%)
Total:	105	63 (60%)	6 (10%)	57 (90%)



Infuvite Adult Correct  
 Incorrect

When examining the interpretations from the written inpatient prescriptions, 5 of 21 (24%) respondents interpreted the name correctly. In addition, 1 of the 19 respondents (5%) from the written outpatient prescriptions interpreted the name correctly. Although three responses were correct for the "Infuvite" portion of the name, the respondents omitted the "Adult" portion of the name. The most common misinterpretation from the inpatient study was *Inquvite Adult*. Other incorrect responses included *Irfuvite Adult*, *Equvite Adult*, *Infovite*, *Infvite Adult*, *Inquvite*, *Inquvite Adult*, *Multivit*, *Myvite Adult* and *Vite Adult*. The most common misinterpretations from the outpatient study were *Insuvate Adult* and *Insurite Adult*. Other incorrect responses included *Insurate Adult*, *Inguvite Adult*, *Insurate*, *Insurate Adult*, *Insuvite Adult* and *Insuvite Adult*. None of the misinterpretations represent names of currently marketed drug products.

Among the verbal outpatient Infuvite Adult prescriptions, all of the respondents interpreted the name incorrectly. However, three responses were correct for the "Infuvite" portion of the name but omitted the "Adult" portion of the name. The misinterpretations for Infuvite Adult included *Invubite*, *Invovite Adult*, *Invovite*, *Invobite Adult*, *Invirite Adult Dose*, *Inflamite*, *Infobit*, *Infobit Adult*, *Infovite*, *Infovite Adult*, *Amphovite Adult*, *Enfluvite Adult*, *Imfovite*, *Imprivite*, *Improvite Adult Dose*, *Improvite Adult*, *Imverite*, *Infavite Adult*, and *Infrovite*, *Vial*. None of the misinterpretations represent names of currently marketed drug products.

### C. ADVERSE EVENT REPORTING SYSTEM (AERS)

A search of the Adverse Event Reporting System (AERS) for medication errors involving INFUVITE% and MVI% resulted in two relevant cases.

ISR# 201333-3 Actual error Event date:  Patient survived	Report from pharmacist who states that a 20 year old woman, 8 weeks pregnant, received 200 mL of M.V.I.-12 within a twenty four hour period. The patient was admitted on _____ for an overnight stay with a diagnosis of nausea and vomiting. The physician ordered 2 separate bags of fluid; 1 vial of MVI to be added to each bag. Two entire multidose vials were mixed (100 mL per 1000 mL bag) and infused. The first bag was infused at 240 mL/hr and the second at 125 mL/hr. The patient was discharged on _____ without problems...
ISR #1994145-3 Actual error Event date:  Unknown outcome	Unverified report from a pharmacist of a "hear say." An infant received the adult formulation of M.V.I.-12 a couple of weeks ago (approximately _____) and experienced a coma for which he/she was treated with UV light. Outcome is unknown.

#### D. DRUG QUALITY REPORTING SYSTEM (DQRS)

In addition, the Drug Quality Reporting System (DQRS) database was searched for error reports with various multivitamins for infusion products. The results of the search included two relevant medication error cases citing confusion between \_\_\_\_\_ and "Pharmacy bulk package" and a scenario involving the vials being connected to the wrong port of the compounder.

113226 113227 Actual error Report date: NOV-18-1993 Unknown location Unknown outcome	Reporter recently encountered a problem with the MVI Pediatric vial and the MVI-12 vial #1 in the compounding area. Reporter used the Baxa TPN compounder and set up all additives for the day at once. A vial of MVI Pediatric was reconstituted and set to the side (yellow cap removed); a vial of MVI-12 was opened (blue cap removed). Technician was interrupted and when they came back the two vials were connected to the wrong ports of the compounder. While this was certainly a failure to read the label correctly, reporter feels that it might be prudent to differentiate these 2 vials with color coding or some more obvious difference in labeling.
050124 Actual error Report date: APR-21-1997 Unknown location Unknown outcome	Because of the labeling, the product is being used inappropriately and creating a potential for infection. The vial is labeled "M.V.I. 12" "Pharmacy bulk package, not for direct infusion." On the side of the vial there is a statement that once the closure system is disturbed, the contents should be used within four hours and the unused portion should be discarded. The reporter, who is a consultant, has found the product stored in the refrigerator dated when it was opened and obviously being used as a multidose vial. Recommendation from reporter to USPC to prevent recurrence: Make the statement that the product has to be discarded four hours after entry bold and easily seen.

#### E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing "Infuvite Adult" and "Infuvite Pediatric", the primary concerns raised by the DMETS expert panel had to do with the safe use of these products in general as well as preventing confusion between adult versus pediatric formulations. In addition there was concern regarding confusion between single dose versus multiple dose formulations. See Appendix A for comparison chart of proposed and approved Infuvite products.

In addition to DMETS Expert Panel Review and Prescription Simulation Studies, DMETS used information from post-marketing medication error reports for Infuvite Adult, Infuvite Pediatric and other injectable multivitamin formulations to identify safety concerns for these proposed names.

##### 1. Proposed Names

The error reports from AERS and DQRS confirmed the concerns raised by DMETS and the concerns regarding the potential for the user to be misled by the word \_\_\_\_\_ in the product names.

The safety issue with \_\_\_\_\_ in the proprietary names is that it misleads the user to think it is a \_\_\_\_\_ . These products are pharmacy bulk packages, and the intention is that the vials are entered one time only.

Many institutions use a standard type of form to guide the prescribing of parenteral nutrition therapy. These forms will typically list "multivitamin" and the recommended volume of that ingredient. The standard form minimizes the opportunity and eliminates the need for a prescriber to order the multivitamin component by a specific brand name. However in one post-marketing error scenario the prescriber ordered "one vial of MVI to each infusion bag". Ultimately this resulted in the administration of 100 mL of multivitamin instead of 10 mL. The same type of scenario can happen when the Infuvite pharmacy bulk package is introduced to the environment where practitioners are already accustomed to using the single dose vial formulation.

## 2. Potential Confusion among the Infuvite Formulations

In addition to the medication error scenarios described by the error reports (See section II.C. and II.D.), there is potential for medication errors involving "Infuvite Adult" or "Infuvite Pediatric Multidose" at the level of purchasing these products from a wholesaler or distributor. The person responsible for buying the drugs in a pharmacy could intend to select the single dose product and actually select the pharmacy bulk package in error, or vice versa. This type of error would depend on how the information is presented (for example a list of all the Infuvite products on the computer screen). The result of such an error is that the person inadvertently introduces a product into the workflow that the practitioners and technicians are not used to preparing. The likelihood for error depends on the previous experience of the technician preparing the drug product and the pharmacist checking the drug product. Although the vial sizes differentiate the single dose and pharmacy bulk package formulations, not all practitioners will have both products in stock to compare them.

There is also opportunity to select the wrong product from the pharmacy shelf if these products are stored next to one another.

## 3. Potential errors with Vial Design

The process of the need to combine vial 1 and vial 2 is also prone to error. There is potential for the omission of one of the vials during the admixture process. The highest risk for these types of errors are when the product is first introduced and unfamiliar to practitioners. There is at least one other adult multivitamin formulation on the market that uses this same technique (Combining Vial 1 and Vial 2). This may decrease the likelihood for error with Infuvite Adult because practitioners are already familiar with the need to combine multiple vials for the preparation of multiple vitamin solutions.

## 4. Potential Dosing Errors

The dosing instructions for the pediatric formulation are

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

In review of the carton labeling, container labels and insert labeling of Infuvite Adult ~~\_\_\_\_\_~~ 4B M and ~~\_\_\_\_\_~~, DMETS has attempted to focus on the safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, in effort to minimize potential user error.

#### A. GENERAL COMMENTS (Infuvite Adult ~~\_\_\_\_\_~~ and Infuvite Pediatric ~~\_\_\_\_\_~~)

1. DMETS is unable to determine how the colors and design of the final printed labels and labeling will impact the likelihood for errors between the adult and pediatric formulations. Currently, the design of the adult and pediatric formulations looks identical. Ensure that there is adequate differentiation in the design of the container and carton labeling for the adult and ~~\_\_\_\_\_~~ formulations to minimize error potential. In addition, ensure the vials do not look like the existing Infuvite products.
2. The ~~\_\_\_\_\_~~ formulations are pharmacy bulk packages. In accordance with the issues raised in the Interim MAPP 7217.1, Uniform Labeling for Pharmacy Bulk Package Dosage Forms, consider the recommendations below.

#### B. CONTAINER LABELS (Infuvite Adult ~~\_\_\_\_\_~~ and Infuvite Pediatric ~~\_\_\_\_\_~~)

1. Currently, the label reads that ~~\_\_\_\_\_~~. However, this is not consistent with a pharmacy bulk package. Revise the statement to read, ~~\_\_\_\_\_~~.
2. If space permits include the date and time the closure was entered. For example,  
~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~
3. If space permits, add a prominent statement to specify that, ~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~
- 4. Add a statement to refer to the package insert for further information on the use of the pharmacy bulk package.
- 5. Add the "Manufactured by:" statement to each container label. Currently the label lists only the "Distributed by:" information.

#### C. CARTON LABELING (Infuvite Adult ~~\_\_\_\_\_~~ and ~~\_\_\_\_\_~~)

See comments in III.B.1, III.B.3, and III.B.4. above.

#### D. INSERT LABELING (Infuvite Adult ~~\_\_\_\_\_~~)

1. PRODUCT TITLE

Add a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion"

Use bold face type, large size type or contrasting color to make this more visible.

2. DESCRIPTION

- a. Consider increases the prominence of "Vial 1" and "Vial 2" in this section to facilitate the identification of the vial contents for each.
- b. Include a general definition of the pharmacy bulk package and a statement indicating the specific uses intended for the container contents. For example, "...a sterile \_\_\_\_\_ contains many single doses \_\_\_\_\_"

3. DOSAGE AND ADMINISTRATION

- a. Currently, the insert reads that the solution should be used  
Revise the statement to read, \_\_\_\_\_
- b. Consider moving the "DIRECTIONS FOR DISPENSING FROM PHARMACY BULK VIAL" section to the DOSAGE AND ADMINISTRATION section.
  - i. Elaborate on the sentence \_\_\_\_\_ Include the maximum time of 4 hours from initial closure entry to complete fluid transfer operations.



**IV. RECOMMENDATIONS**

A. DMETS does not recommend the use of the word " \_\_\_\_\_ " in the proprietary name, Infuvite Adult

B. DMETS does not recommend the use of the word " \_\_\_\_\_ " in the proprietary name,

C. DMETS recommends implementation of the labeling revisions described in Section III.

D. DDMAC \_\_\_\_\_

DMETS 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 Sammie Beam at 301-827-3242.

\_\_\_\_\_ **S**  
Marci Lee, PharmD  
Safety Evaluator  
Division of Medication Errors and Technical Support (DMETS)

Concur: \_\_\_\_\_ **S**

\_\_\_\_\_ **S**  
Denise Toyer, PharmD                      Date  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

## Appendix A - Infuvite Product Line

Product Name	Dosage form(s)	Generic name	Usual dose*	Proposed or Approved
Infuvite Pediatric				Proposed NDA 21-646
Infuvite Adult	Multiple Vitamins for Infusion Pharmacy Bulk Package Vial 1 is 50 mL and Vial 2 is 50 mL fill in 100 mL Combine vial 1 and vial 2		Adults and children 11 years and older: Daily dose of 10 mL should be added to not less than 500 mL of intravenous infusion solution.	Proposed NDA 21-559
Infuvite Pediatric	Multiple Vitamins for Infusion Boxes containing 2 vials: Vial 1 is 4 mL Vial 2 is 1 mL Also boxes containing 5 of each vial (10 vials total)		Less than 1 kg: 1.2 mL of vial 1 and 0.3 mL of vial 2 Between 1 kg and 3 kg: 2.6 mL of vial 1 and 0.65 mL of vial 2 Greater than or equal to 3 kg up to 11 years: Daily dose (4 mL of vial 1 and 1 mL of vial 2) should be added directly to not less than 100 mL of intravenous dextrose, saline or similar infusion solutions.	Approved FEB-21-2001 NDA 21-265
Infuvite Adult	Multiple Vitamins for Infusion Boxes containing 2 vials: Vial 1 is 5 mL Vial 2 is 5 mL Also boxes containing 5 of each vial (10 vials total)		Adults and children 11 years and older: 5 mL of vial 1 plus 5 mL of vial 2 added directly to not less than 500 mL of intravenous infusion solution.	Approved MAY-18-2000 NDA 21-163

\* Frequently used, not all inclusive

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this page is the manifestation of the electronic signature.**

/s/

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Marci Ann Lee  
5/16/03 12:59:56 PM  
PHARMACIST

Denise Toyer  
5/16/03 01:02:01 PM  
PHARMACIST

Carol Holquist  
5/16/03 01:09:42 PM  
PHARMACIST

Jerry Phillips /  
5/16/03 01:33:23 PM  
DIRECTOR

# REQUEST FOR CONSULTATION

Division/Office):

FROM: David B. Lewis, Ph.D.

Mail: ODS (Room 15B-08, PKLN Bldg.)

DATE: February 13<sup>th</sup>, 2003

IND NO.

NDA NO. 21-559

TYPE OF DOCUMENT: Original NDA

DATE OF DOCUMENT: Submitted August 14<sup>th</sup>, 2002. 10-month date: 6-16-03.

NAME OF DRUG: INFUVITE ADULT

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE:  
April 2003

NAME OF FIRM: Sabex Inc., 145 Jules-Leger, Boucherville, QC, CANADA J4B 7K8

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW)         |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

### II. BIOMETRICS

#### STATISTICAL EVALUATION BRANCH

#### STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: NDA 21-559 is the pharmacy bulk packaged version of INFUVITE ADULT, which is filed under NDA 21-163. Please evaluate the proposed proprietary name: INFUVUTE ADULT along with the labeling, especially, that labeling which pertains to the dispensing instructions for the pharmacy bulk package. The aluminum label statement has not yet been determined by data; however, the implementation date for this labeling (as required by 21 CFR 201.323) has been pushed back to January 26<sup>th</sup>, 2004.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

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David Lewis  
2/13/03 10:40:31 AM

46

Draft Labeling Page(s) Withheld

# General Chapters

## General Tests and Assays

### General Requirements for Tests and Assays

#### (1) INJECTIONS

##### INTRODUCTION

Parenteral articles are preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they contain are administered, using gravity or force, directly into a blood vessel, organ, tissue, or lesion. Parenteral articles are prepared scrupulously by methods designed to ensure that they meet Pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of the growth of microorganisms. An Injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration.

##### NOMENCLATURE AND DEFINITIONS

###### Nomenclature

The following nomenclature pertains to five general types of preparations, all of which are suitable for, and intended for, parenteral administration. They may contain buffers, preservatives, or other added substances.

1. [DRUG] Injection—Liquid preparations that are drug substances or solutions thereof.
2. [DRUG] for Injection—Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections.

This nomenclature has been adopted by the USP Drug Nomenclature Committee for implementation by supplemental revisions of USP 23-NF 18. For ready official monograph titles in the form *Sterile [DRUG]* that have not been revised, the following nomenclature continues in use in this Pharmacopeia: (1) medicaments or solutions or emulsions thereof suitable for injection bearing titles of the form [DRUG] Injection; (2) dry solids or liquid preparations containing no buffers, diluents, or other added substances, and which, upon the addition of suitable solvents, yield solutions conforming in all respects to the requirements for Injections, and which are distinguished by titles of the form *Sterile [DRUG]*; (3) preparations the same as those described in (2) except that they contain one or more buffers, diluents, or other added substances, and which are distinguished by titles of the form [DRUG] for Injection; (4) solids which are suspended in a suitable fluid medium and which are injected intravenously or into the spinal canal, distinguished by titles of the form *Sterile [DRUG] Suspension*; and (5) dry solids which, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Sterile Suspensions, and which are distinguished by titles of the form *Sterile [DRUG] for Suspension*.

3. [DRUG] *Injectable Emulsion*—Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium.

4. [DRUG] *Injectable Suspension*—Liquid preparations of solids suspended in a suitable liquid medium.

5. [DRUG] *for Injectable Suspension*—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for *Injectable Suspensions*.

##### Definitions

###### PHARMACY BULK PACKAGE

A *Pharmacy bulk package* is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes.

The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set which allows measured dispensing of the contents. The *Pharmacy bulk package* is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

Designation as a *Pharmacy bulk package* is limited to preparations from *Nomenclature* categories 1, 2, or 3 as defined above. *Pharmacy bulk packages*, although containing more than one single dose, are exempt from the multiple-dose container volume limit of 30 mL and the requirement that they contain a substance or suitable mixture of substances to prevent the growth of microorganisms.

Where a container is offered as a *Pharmacy bulk package*, the label shall (a) state prominently "Pharmacy Bulk Package—Not for direct infusion," (b) contain or refer to information on proper techniques to help assure safe use of the product, and (c) bear a statement limiting the time frame in which the container may be used once it has been entered, provided it is held under the labeled storage conditions.

###### LARGE- AND SMALL-VOLUME INJECTIONS

Where used in this Pharmacopeia, the designation *Large-volume intravenous solution* applies to a single-dose injection that is intended for intravenous use and is packaged in containers labeled as containing more than 100 mL. The designation *Small-volume Injection* applies to an Injection that is packaged in containers labeled as containing 100 mL or less.

##### BIOLOGICS

The Pharmacopeial definitions for sterile preparations for parenteral use generally do not apply in the case of the biologics because of their special nature and licensing requirements (see *Biologics* (1041)).

Dated: April 13, 2000.

Nancy Cheal,  
Acting Associate Director for Policy,  
Planning, and Evaluation, Centers for Disease  
Control and Prevention (CDC).

[FR Doc. 00-9886 Filed 4-19-00; 8:45 am]

BILLING CODE 4163-18-P

**DEPARTMENT OF HEALTH AND  
HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. 79N-0113; DESI 2847]

**Parenteral Multivitamin Products;  
Drugs for Human Use; Drug Efficacy  
Study Implementation; Amendment**

**AGENCY:** Food and Drug Administration,  
HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the conditions for marketing an effective adult parenteral multivitamin drug product that published in the Federal Register of September 17, 1984 (49 FR 36446). The agency is notifying manufacturers of modifications in the adult formulation and certain portions of the labeling for the products.

**DATES:** Supplements to approved new drug applications (NDA's) and abbreviated new drug applications (ANDA's) are due on or before June 19, 2000.

**ADDRESSES:** Communication in response to this notice should be identified with the reference number DESI 2847 and

directed to the attention of the appropriate office named below.

Supplements to full NDA's (identify with NDA number): Division of Metabolic and Endocrine Drug Products (HFD-510), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Original ANDA's: Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

Requests for opinion of the applicability of this notice to a specific product: Division of Prescription Drug Compliance and Surveillance (HFD-330), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

**FOR FURTHER INFORMATION CONTACT:**

Mary E. Catchings, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

**SUPPLEMENTARY INFORMATION:** In a notice published in the Federal Register of September 17, 1984 (49 FR 36446), FDA announced the conditions for marketing an effective parenteral multivitamin preparation. The effective 12-vitamin formulation set forth in the notice was based on the clinical evaluation of a guideline formulation recommended in 1975 by the American Medical Association (AMA). The notice also stated that, because parenteral

multivitamin products are used and evaluated in patients with a variety of disease conditions, future adjustments to the formulation may be necessary.

On August 21, 1985, FDA's Division of Metabolic and Endocrine Drug Products and the AMA's Division of Personal and Public Health Policy sponsored a public workshop on "Multivitamin Preparations for Parenteral Use." At the workshop, additional data from clinical testing of the 1975 AMA formulation and a variety of other data were presented and discussed in light of available information on parenteral vitamin therapy. After examining the data, the AMA-FDA workshop committee recommended that the dosage of vitamins B<sub>1</sub>, B<sub>6</sub>, C, and folic acid be increased and that vitamin K be added to the formulation. Based on a review of the committee's recommendations, the Director of the Center for Drug Evaluation and Research has concluded that the 1975 AMA formulation for parenteral multivitamins should be modified to reflect the advice of the committee.

Accordingly, this notice amends portions of the section *Conditions for Approval and Marketing* in the September 17, 1984, notice as follows (in accordance with current labeling practice, amounts previously listed in international units (IU) have been converted to weights):

Paragraph 1(a)(i) is revised as follows:

1. *Adult formulation (intended for ages 11 and older)*

Ingredient	Amount per Unit Dose
<b>Fat Soluble Vitamins</b>	
A (retinol)	1 milligram (mg)
D (ergocalciferol or cholecalciferol)	5 micrograms (µg)
E (alpha-tocopherol)	10 mg
K (phyloquinone)	150 µg
<b>Water-Soluble Vitamins</b>	
C (ascorbic acid)	200 mg
Folic acid	600 µg
Niacin	40 mg
B <sub>2</sub> (riboflavin)	3.6 mg
B <sub>1</sub> (thiamine)	6.0 mg
B <sub>6</sub> (pyridoxine)	6.0 mg
B <sub>12</sub> (cyanocobalamin)	5 µg
Pantothenic acid	15.0 mg
Biotin	60 µg

**2. Labeling conditions.**

(a) The label must bear the statement "Rx only."

(b) *Indication.* Paragraph 2(b)(i)(a) is revised as follows (This language may be editorially adapted to a specific product's labeling, as appropriate.):

*Adult.* This formulation is indicated as a daily multivitamin maintenance dosage for adults and for children age 11 and above receiving parenteral

nutrition. It is also indicated in other situations where intravenous administration is required. Such situations include surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states, which may provoke a stress situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. This product (administered in intravenous fluids under proper dilution) contributes intake of these vitamins that are necessary toward maintaining the body's normal resistance and repair processes.

The physician should not await the development of clinical signs of vitamin deficiency before initiating vitamin therapy.

Patients with multiple vitamin deficiencies or with markedly increased requirements may be given multiples of the daily dosage for 2 or more days, as indicated by the clinical status. Clinical testing indicates that some patients do not maintain adequate levels of certain vitamins when this formulation in recommended amounts is the sole source of vitamins.

**(c) Contraindications:**

Known hypersensitivity to any of the vitamins or excipients in this product or a preexisting hypervitaminosis. Allergic reaction has been known to occur following intravenous administration of thiamine and vitamin K. The formulation is contraindicated prior to blood sampling for detection of megaloblastic anemia, as the folic acid and the cyanocobalamin in the vitamin solution can mask serum deficits.

In addition, the following sections required by 21 CFR 201.57 should read as follows:

1. **Precautions:** (The following paragraph should be added and should appear in bold type.)

Caution should be exercised when administering this multivitamin formulation to patients on warfarin sodium-type anticoagulant therapy. In such patients, periodic monitoring of prothrombin time is essential in determining the appropriate dosage of anticoagulant therapy.

2. **Drug Reactions:** This section is revised to read "Drug Interactions" and to add aminophylline 125 mg and ampicillin 500 mg to this list.

Supplements to approved NDA's or ANDA's providing for appropriate revision of the labeling of drug products affected by this notice should be submitted on or before June 19, 2000.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 201(n), 502, 505, 52 Stat. 1041, 1050-1053, as amended (21 U.S.C.

321(n), 352, 355)) and under the authority delegated to the Director of the Center for Drug Evaluation and Research (21 CFR 5.70).

Dated: March 28, 2000.

Janet Woodcock,  
Director, Center for Drug Evaluation and Research.

[FR Doc. 00-9848 Filed 4-19-00; 8:45 am]

BILLING CODE 4160-01-F

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

**Name of Committee:** General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee.

**General Function of the Committee:** To provide advice and recommendations to the agency on FDA's regulatory issues.

**Date and Time:** The meeting will be held on May 8, 2000, 8 a.m. to 5 p.m.

**Location:** Marriott Washingtonian Center, Salons F and G, 9751 Washingtonian Blvd., Gaithersburg, MD.

**Contact Person:** David Krause, Center for Devices and Radiological Health (HFZ-410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-3090, ext. 141, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12519. Please call the Information Line or access the Internet at <http://www.fda.gov/cdrh/panelmtg.html> for up-to-date information on this meeting.

**Agenda:** The committee will discuss, make recommendations, and vote on two premarket approval applications for: (1) An in situ polymerizable surgical mesh intended to be used to seal air leaks following thoracic cavity surgery; and (2) an interactive wound and burn dressing intended to be used for the treatment of diabetic foot ulcers.

**Procedure:** Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact

person by May 1, 2000. Oral presentations from the public will be scheduled between approximately 8:15 a.m. and 8:45 a.m., 11:15 a.m. and 11:45 a.m., 1:15 p.m. and 1:45 p.m., and 4 p.m. and 4:30 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before May 1, 2000, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

FDA regrets that it was unable to publish this notice 15 days prior to the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee meeting. Because the agency believes there is some urgency to bring these issues to public discussion and qualified members of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee were available at this time, the Commissioner of Food and Drugs concluded that it was in the public interest to hold this meeting even if there was not sufficient time for the customary 15-day public notice.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: April 14, 2000.

Linda A. Suydam,  
Senior Associate Commissioner.  
[FR Doc. 00-9908 Filed 4-19-00; 8:45 am]  
BILLING CODE 4160-01-F

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### Neurological Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

**Name of Committee:** Neurological Devices Panel of the Medical Devices Advisory Committee.

**General Function of the Committee:** To provide advice and recommendations to the agency on FDA's regulatory issues.

Council on Historic Preservation, 1522 K Street NW., Washington, D.C. 20005, 202-254-3974.

Robert R. Garvey, Jr.,  
Executive Director.

FR Doc. 79-21472 Filed 7-12-79; 8:45 am]  
BILLING CODE 4310-10-M

**DEPARTMENT OF HEALTH,  
EDUCATION, AND WELFARE**

**Food and Drug Administration**

[Docket No. 79P-012]

**Abbott Laboratories; Panel  
Recommendation on Petition for  
Reclassification**

**Correction**

In FR Doc. 79-16991 appearing at page 31714 in the issue for Friday, June 1, 1979 make the following corrections:

(1) On page 31715 column one "Summary of Data on Which the Recommendation is Based" paragraph 2, line 9, "PH4" should appear as "PF4".

(2) On page 31715 column two, paragraph 3, line 3 "PH4" should appear as "PF4".

(3) On page 31715 column two, paragraph 5, lines 9 and 14 "PH4" should appear as "PF4", and in line 13 "thromboglobulin" should appear as "thromboglobulin".

BILLING CODE 1605-01-M

[Docket No. 79N-0138]

**American Cyanamid Co.; Withdrawal of  
Approval of NADA for Cyzine Premix**

AGENCY: Food and Drug Administration.  
ACTION: Notice.

**SUMMARY:** The agency withdraws approval of a new animal drug application (NADA) providing for use of Cyzine Premix 10% (containing 2-acetylamino-5-nitrothiazole) in turkey feed as an aid in prevention of blackhead. The sponsor, American Cyanamid Co., requested this action. EFFECTIVE DATE: July 23, 1979.

**FOR FURTHER INFORMATION CONTACT:** David N. Scarr, Bureau of Veterinary Medicine (HFV-214), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3183.

**SUPPLEMENTARY INFORMATION:** American Cyanamid Co., P.O. Box 400, Princeton, NJ 08540, is sponsor of NADA 9424 which provides for use of Cyzine remix 10% in turkey feed as an aid in prevention of blackhead (histomoniasis).

The application was originally approved July 21, 1954. By letter of February 16, 1979, the firm requested that approval of the NADA be withdrawn because the product is no longer being marketed.

Published elsewhere in this issue of the Federal Register is a final order revoking § 558.25 2-Acetylamino-5-nitrothiazole (21 CFR 558.25) to reflect withdrawal of approval of this application.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(e), 82 Stat. 345-347 (21 U.S.C. 380b(e))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1) and redelegated to the Director of the Bureau of Veterinary Medicine (21 CFR 5.84), and in accordance with § 514.115 *Withdrawal of approval of applications* (21 CFR 514.115), notice is given that approval of NADA 9424 and all supplements for Cyzine Premix 10% is hereby withdrawn, effective July 23, 1979.

Dated: July 6, 1979.

Terence Hervey,

Director, Bureau of Veterinary Medicine.

FR Doc. 79-21502 Filed 7-12-79; 8:45 am]  
BILLING CODE 4110-03-M

[Docket No. 78F-0141]

**Marshall Minerals, Inc.; Order Denying  
Petition for Food Additive Regulation  
on Gentian Violet; Extension of Time  
for Filing Data**

AGENCY: Food and Drug Administration.  
ACTION: Notice.

**SUMMARY:** This notice extends the time for filing data to support a request for hearing on the order of denial of a petition proposing to establish a regulation to permit the safe use of gentian violet.

**DATE:** Data to be filed by August 3, 1979.

**ADDRESS:** Data to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Lonnie W. Luther, Bureau of Veterinary Medicine (HFV-147), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4317.

**SUPPLEMENTARY INFORMATION:** The Food and Drug Administration (FDA) is extending to August 3, 1979 the time for filing data to support a request for hearing on the order published in the Federal Register of March 30, 1979 (44 FR 19035), on the denial of a petition proposing to establish a regulation to

permit the safe use of gentian violet in animal feed.

The March 30, 1979 order gave interested persons until April 30, 1979 to file the data. Marshall Minerals, Inc., P.O. Box 506, Bainbridge, GA 31717, has requested additional time to respond to the subject order. Because of the amount of scientific material which must be reviewed and evaluated, FDA is granting the request.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 409(c)(1)(B), (e), (f), 72 Stat. 1786-1787 (21 U.S.C. 348(c)(1)(3), (e), (f)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), the time for filing data to support requests for a hearing on the subject order is extended to August 3, 1979.

Dated: July 6, 1979.

William F. Randolph,

Acting Associate Commissioner for  
Regulatory Affairs

FR Doc. 79-21500 Filed 7-12-79; 8:45 am]  
BILLING CODE 4110-03-M

[Docket No. 79N-0113; DESI 2647]

**Parenteral Multivitamin Products;  
Drugs for Human Use; Drug Efficacy  
Study Implementation; Permission for  
Drugs To Remain on the Market**

AGENCY: Food and Drug Administration.  
ACTION: Notice.

**SUMMARY:** The Food and Drug Administration announces changes in the previously published conditions for marketing parenteral multiple vitamin preparations that have been allowed to remain on the market until appropriate formulations of such products could be agreed upon. The changes now being made require that manufacturers submit new drug applications (NDA's) or supplemental applications for reformulated products and test them in accordance with the criteria in this notice.

**DATE:** New drug applications (or supplemental new drug applications) must be submitted by October 11, 1979.

**ADDRESSES:** Responses to this notice should be identified with the NDA number (if any) and the following in a box in the upper portion of the cover letter: "Paragraph XIV Drug—Category XI (Parenteral Multivitamins)", directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

New drug applications (identify with NDA number): Documents and Records

Section (HFD-106), Rm. 8B-45, Bureau of Drugs.

Supplements to new drug applications (identify with NDA number): Division of Metabolism and Endocrine Drug Products (HFD-120), Rm. 12B-63, Bureau of Drugs.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD-501), Bureau of Drugs.

**FOR FURTHER INFORMATION CONTACT:**  
Wald Y. Brody, Team of Drugs (HFD-130), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3520.

**SUPPLEMENTARY INFORMATION:** In a notice (DESI 2647) published in the Federal Register of July 27, 1972 (37 FR 15027) FDA announced its conclusion that, as currently formulated, parenteral multivitamin preparations lack substantial evidence of effectiveness for their claimed indications.

It is recognized that parenteral multivitamin therapy is essential in preventing or treating hypovitaminoses in certain disease states or postoperative conditions. The conclusion of lack of substantial evidence of effectiveness was not based upon lack of effectiveness of individual vitamins, but upon the finding that formulations now available lack certain essential vitamins, or contain too much or too little of other vitamins, or both. Because of the critical medical importance of parenteral multivitamin therapy and lack of alternative drugs, the Commissioner of Food and Drugs concluded that these products should remain available as presently formulated, to allow time to resolve the complex technical and medical problems and to develop and test rational formulations of parenteral multivitamin preparations. That conclusion was published in the Federal Register of December 14, 1972 (37 FR 26623). Formulations that are now believed to be rational ones and guidelines for their clinical study are now available. The notice that follows describes them in detail and specifies the conditions for continued marketing of presently marketed products while studies of appropriately reformulated products are in progress.

In the final report to the Commissioner on the Drug Efficacy Study by the National Academy of

Sciences-National Research Council, Division of Medical Sciences, the Panel on Drugs Used in Endocrine Disturbances and the Panel on Drugs Used in Metabolic Disorders stated as follows:

"The Panel does not recognize the need for multi-vitamin supplementation in healthy individuals who have an adequate diet. However, the Panel does recognize the need for multiple-vitamin and mineral preparations in certain segments of the population. It also recognizes the lack of precise data on which rational formulation can be based. Therefore, it takes the following position toward all such preparations:

- "1. All should be appropriately labeled as either 'supplemental' or 'therapeutic.'
- "2. The formulations of supplemental preparations should be based on dietary allowances recommended either by the Food and Nutrition Board of the National Academy of Sciences or by an equivalent body.
- "3. Any preparations labeled 'therapeutic' should be so formulated that the physician can prescribe adequate therapeutic amounts without the danger of toxicity.
- "4. The preparations should not contain disproportionate amounts of any nutrient that could be potentially hazardous in the recommended dosage. The recommended dosage and labeling for any fat-soluble vitamin should include proper warning concerning possible toxicity.
- "5. The preparations should not contain non-essential materials.
- "6. The Panel favors the use of oral preparations when it is feasible to use such formulations."

In October 1972, the American Medical Association (AMA) offered to assist FDA in determining rational formulations for parenteral multivitamins and in developing guidelines for studies concerning their stability, safety, and effectiveness. In December 1975, the AMA submitted its report entitled "Guidelines for Multivitamin Preparations for Parenteral Use." With certain minor exceptions, i.e., concerning the nomenclature for folic acid, the duration of clinical studies, and disease states in which clinical studies are required, FDA accepts the recommendations contained in the report. These exceptions are dealt with in the notice below. The report constitutes the scientific basis for this notice. The verbatim text of the report is on file with and may be seen in the office of the FDA Hearing Clerk, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday. Single copies of the report are available from the Hearing Clerk at the above address.

The following parenteral multivitamin products were reviewed in the Drug Efficacy Study and were named in the notices of July 27, 1972, and December

14, 1972. These products and identical, similar, or related products, whether or not they are now the subject of an approved new drug application (NDA), may remain on the market as presently formulated, under the conditions specified below, pending completion of studies necessary to determine the stability, safety, and effectiveness of appropriately reformulated products. It is recognized that the composition of a product being allowed to continue on the market may differ substantially from the one being studied. However, this is necessary in order to assure that parenteral multivitamin products remain available to fulfill the critical medical need. Therefore, category XI Parenteral Multivitamin Products, published in the notice of December 14, 1972, is amended to read as follows:

#### XI. Parenteral Multivitamin Products

1. NDA 4-895: Breonex L Injectable, and
2. Breonex M Injectable, both containing thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, panthenol, niacinamide, and cyanocobalamin; Cooper Laboratories, 1300 Fairfield Rd., Wayne, NJ 07470.
3. NDA 4-835: Declysyl Injectable containing dextrose, sodium chloride, thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, and cyanocobalamin; Abbott Laboratories, 14th and Sheridan Rd., North Chicago, IL 60064.
4. NDA 4-895: Parbexin Injectable containing thiamine hydrochloride, niacinamide, dexpanthenol, riboflavin, and pyridoxine hydrochloride; Smith, Miller & Patch, Division of Cooper Laboratories, P.O. Box 367, San German, Puerto Rico 00753.
5. NDA 8-071: Berocca-C Injectable, and
6. Berocca-C 500 Injectable, both containing thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, dexpanthenol, d-biotin, and ascorbic acid; Roche Laboratories, Division of Hoffmann-LaRoche, Inc., Roche Park, Nutley, NJ 07110.
7. NDA 8-141: Folbesyn Injectable containing thiamine hydrochloride, sodium panthothenate, niacinamide, riboflavin, pyridoxine, cyanocobalamin, ascorbic acid, and folic acid; Lederle Laboratories, Division of American Cyanamid Co., P.O. Box 500, Pearl River, NY 10985.
8. NDA 8-373: Vi-Syneral Injectable containing vitamin A, ergocalciferol, ascorbic acid, thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, dexpanthenol, dl-alpha tocopherol acetate; USV Pharmaceuticals Corp., 2 Scarsdale Rd., Tuckahoe, NY 10707.
9. NDA 7-500: Manubee Injectable containing thiamine hydrochloride, niacinamide, dexpanthenol, pyridoxine hydrochloride, and riboflavin, and
10. Manubee-C 500 Injectable containing thiamine hydrochloride, niacinamide, dexpanthenol, pyridoxine hydrochloride, riboflavin, and ascorbic acid; Endic Laboratories, Inc., Subsidiary of E. I. duPont

Nemours & Co., Inc., 1000 Stewart Ave., Garden City, NY 11530.

11. NDA 7-819: Betolake Improved Injectable containing thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, and dexpantenol; Lakeside Laboratories, Inc., 1707 East North Ave., Milwaukee, WI 53201.

12. NDA 8-809: M.V.I. Injectable containing ascorbic acid, vitamin A, ergocalciferol, thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, dexpantenol, and dl-alpha tocopherol acetate; U.S.V. Pharmaceutical Corp.

13. NDA 7-094: Soluzyne Injectable containing cyanocobalamin, folic acid, thiamine hydrochloride, sodium pantothenate, and niacinamide; The Upjohn Co., 7171 Portage Rd., Kalamazoo, MI 49002.

The specific conditions for marketing parenteral multivitamin products are as follows:

*A. Requirements for Products (as Presently Formulated) on the Market on July 13, 1979, Whether or Not Provided for in New Drug Applications*

Proceedings to withdraw approval of NDA's (for presently formulated products) that have approved or "deemed approved" status on July 13, 1979, or to take regulatory action to remove from the market products that are not subjects of approved or "deemed approved" new drug applications, will not be initiated provided that the following conditions are met:

1. On or before October 11, 1979, the manufacturer of any such product must submit a new drug application (NDA) (if currently marketed formulation is not now provided for in an NDA) or, if the currently marketed formulation is now the subject of an approved or "deemed approved" application, must supplement the NDA outlining the steps to fulfill these requirements. This plan must include: (a) the formulation(s) proposed for marketing, (b) the stability and biological availability studies proposed on this formulation(s), and (c) the general format of the clinical studies proposed on this formulation(s).

a. Product(s) must be formulated to be in accord with a formulation(s) recommended in the AMA report above except that the term "folacin" is replaced by the more specific nomenclature "folic acid."

b. Proposed studies of stability and biological availability of vitamins in the finished formulation must include those recommended in the AMA report above (Parts V, C and D). The amount of each vitamin added to provide, at the end of shelf life, a potency not less than 90 percent of that claimed on the label must not exceed 125 percent of the amount claimed on the label. Strict

limitation of overage is necessary to ensure: (1) that the formulation does not contain potentially toxic amounts of any vitamin, the fat-soluble vitamins being of the most concern, and (2) that a physician can, with reasonable certainty, determine from the label the amount of each vitamin to be received by the patient at the beginning as well as the end of shelf life. If an applicant believes that the above overage limit is not feasible for one or more of the vitamins, then data documenting this should be submitted.

c. The plan for clinical studies proposed must be in accord with the guidelines set forth in the AMA report above. Although highly desirable, testing of the formulation(s) in patients from each of the categories listed in Table 5 of the AMA report is not required. However, at least two adequate and well-controlled clinical trials are required for each intravenous formulation, and the number of patients studied must be sufficient for clear demonstration of effectiveness.

Formulations to be marketed for adults must be tested in adults. Formulations to be marketed for children must be tested in both neonates and older children.

Determining the duration of a clinical study should take into account the duration of use reasonably expected in patients who will receive the formulation(s) when it is generally marketed.

Testing of a formulation for intramuscular administration that is indicated for brief clinical use may be limited to a clinical bioavailability study designed to demonstrate the equivalence of this formulation with a formulation for intravenous use, after clinical effectiveness and safety of the intravenous formulation have been studied.

Formulations for intravenous use should ideally be studied for the length of time necessary for depletion of body stores to the extent sufficient to produce decreasing blood/urine levels. Since such studies would be lengthy for some of the vitamins, such as vitamin B<sub>12</sub> and the fat-soluble vitamins, they are not required. However, the formulation(s) may be the only source of vitamins for patients receiving total parenteral nutrition for many months or years. For this reason, studies of at least 4 months' duration and preferably of 6 months are required for at least one group of patients in this category; patients who require maintenance vitamins as part of long-term total parenteral nutrition.

Methodology in the field of vitamin assays in developing rapidly. If a

manufacturer has reason to believe that an assay of: (1) a vitamin in a body fluid other than or in addition to the one(s) given in the AMA report, (2) a different assay method, or (3) a vitamin transport protein is a more accurate indicator of body stores, then this information should be submitted.

2. NDA's and supplements must be in organized form with sequential page numbers, a detailed table of contents referenced to the relevant pages, and tabulations, summaries, and discussion of the data. Otherwise they will be rejected.

3. The Bureau of Drugs will review submitted applications and approve or comment on the plan within 60 days. Within 60 days of receiving any comments from the Bureau, the applicant must respond; the Bureau will give final approval or disapproval of the plan within 60 days of this response. Plans disapproved at this step may be submitted in the usual manner as part of a Notice of Claimed Investigational Exemption for a New Drug (IND) for the proposed product and will be handled under the usual IND/NDA procedures. Within 6 months after receipt of the Bureau's approval of the plan, the applicant must submit data on stability and biological availability, other relevant chemistry and manufacturing information, and detailed protocols for clinical studies in the form of an amendment to the NDA or NDA supplement. The Bureau will review and "conditionally approve" it if satisfactory. The product may then be marketed.

4. Within 90 days after receiving conditional approval, the applicant must begin the clinical trials discussed in 3(c) above, and must report the results of the trials to the Bureau of Drugs within one year after the date of conditional approval. The application will then be approved if satisfactory. Subsequent modifications of formulations on the basis of the results of clinical trials will be handled as supplements to approved NDA's.

5. Manufacturers of products containing the same ingredients at the same dosages or dosage ratios are encouraged to conduct studies in cooperation with one another and to submit joint protocols for clinical trials.

*B. Requirements for Products Entering the Market After July 13, 1979.*

Regulatory action will be taken against any such product that enters the market after July 13, 1979, that is not the subject of an approved or conditionally approved new drug application.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 505).

701, 52 Stat. 1052-1053, as amended 1055-1068, as amended, (21 U.S.C. 355, 371)) and the Administrative Procedure Act (5 U.S.C. 553, 554), and under authority delegated to the Commissioner (21 CFR 5.1).

Dated: July 4, 1979.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

(FR Doc. 79-2301 Filed 7-12-79; 8:45 am)

BILLING CODE 0110-02-08

(Docket No. 78H-0325; DESI 3265)

**Certain Anticholinergic Drugs; Withdrawal of Approval of New Drug Applications**

AGENCY: Food and Drug Administration (FDA).

ACTION: Notice.

**SUMMARY:** This notice withdraws approval of 15 anticholinergic drugs. The basis for the withdrawal is the election of the sponsors to neither contest the findings of the Food and Drug Administration that the drugs lack substantial evidence of effectiveness for certain indications, nor submit supplements showing (1) deletions of those indications from their labeling, and (2) updating of their new drug applications. The drug products are no longer marketed.

**EFFECTIVE DATE:** July 23, 1979.

**ADDRESSES:** Requests for an opinion of the applicability of this notice to specific drug product should be directed to the Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Carol A. Kimbrough, Bureau of Drugs (HFD-32), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

**SUPPLEMENTARY INFORMATION:** In the Federal Register of March 22, 1977 (42 FR 15465), FDA reclassified the probably and possibly effective indications of certain anticholinergic drugs to lacking substantial evidence of effectiveness and offered an opportunity for hearing concerning their reclassification. For those firms not requesting a hearing, but electing to retain their new drug applications (s), the notice required the submission of (1) a supplement for labeling revised in accordance with the notice and (2) a supplement updating the

new drug application. Approval of the following new drug applications, for which sponsors elected to neither

request a hearing nor submit the requested supplements, is now being withdrawn:

NDA No.	Drug	NDA holder
3-266	Menopace Tablets, Hypodermic Tablets, Drops, Elixir and Injection, each containing methylatropine tartrate.	Perrinell P. Macaron Product Division, P.O. Box 1104, Rochester, NY 14603
8-398	Parental Injection containing diphenhydramine hydrochloride.	Schering Corp., Kenilworth, NJ 07033
8-402	That part pertaining to Atrerenyl Bromide Pediatric Drops and Syrup, each containing oxyphenonium bromide.	Ciba Pharmaceutical Co., Division of Ciba-Geigy Corp., 568 Morris Ave., Summit, NJ 07901
8-885	Cerazone Tablets and Elixir, each containing amphetamine sulfate.	Bristol Laboratories, Division of Bristol-Meyers Co., Box 657, Syracuse, NY 13201
9-427	That part pertaining to Pipital Capsules and Elixir, each containing pipizolate bromide.	Marrell Medical Laboratories, Division of Richardson-Merrell, Inc., 110 E. Army Rd., Cincinnati, OH 45215
9-757	Pamine Syrup containing methocyclopamine bromide.	The Upjohn Co., 7171 Portage Rd., Kalamazoo, MI 49002
8-888	Eltroxine Chloride Tablets containing tri-cyclohexyl ethane, and Eltroxine Sulfate Tablets containing tri-cyclohexyl sulfate.	Eli Lilly & Co., P.O. Box 010, Indianapolis, IN 46206
8-890	That part pertaining to Tricoloid Tablets containing tri-cyclohexyl ethane.	Burroughs Wellcome & Co., 3000 Cornerstone Rd., Research Triangle Park, NC 27709
9-032	Monodal Bromide Caplets and Elixir, each containing pentobarbital bromide.	Winthrop Laboratories, Division of Sterling Drug Inc., 90 Park Ave., New York, NY 10016
8-854	Diazin Sulfate Injection containing dibutyltin sulfide.	Merck & Co., Inc., West Point, PA 19380
11-037	That part pertaining to Tral Drops containing hexocyclidol hydrochloride.	Abbott Laboratories, Abbott Park, 14th & Snowden Rd., North Chicago, IL 60064
9-001	Atrerenyl Bromide Injection containing oxyphenonium bromide.	Ciba Pharmaceutical Co., Division of Ciba-Geigy Corp., 568 Morris Ave., Summit, NJ 07901
10-281	Monodal Tablets containing pentobarbital bromide.	Winthrop Laboratories, Inc., 90 Park Ave., New York, NY 10016
8-494	Meltran Tablets containing hemetropine acetylhydrochloride.	Perrinell Corp.
13-429	Valgen Elixir containing entostopine methylbromide.	Endo Laboratories, Inc., 1000 Stewart Ave., Garden City, NY 11533

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the applications reviewed and are subject to this notice under § 310.8 (21 CFR 310.8). Any person who wishes to determine whether a specific product is covered by this notice, should write to the Division of Drug Labeling Compliance (address given above).

The following new drug application was also named in the notice of March 22, 1977.

NDA No.	Drug	NDA holder
9-409	That part pertaining to Pathilon Tablets and Pathilon Parenteral containing methoxyethyl chloride.	Lederle Laboratories, Div. of American Cyanamid Co., P.O. Box 2001, Parsippany, NJ 07054

The sponsor of that new drug application submitted a request for hearing that FDA is now reviewing. Marketing of the drug products Pathilon Tablets and Pathilon Parenteral, for which the hearings request is under review, may continue pending a ruling on the request. (Several other hearing request were filed but later withdrawn by sponsors who then submitted revised labeling in accord with the requirement in the Federal Register notice of March 27, 1977.)

There are no other outstanding hearing requests filed in response to the March 22, 1977 notice. The failure to file

such an appearance constitutes election not to avail oneself of the opportunity for a hearing.

The Director of the Bureau of Drugs, under the Federal Food, Drug, and Cosmetic Act, (sec. 505, 52 Stat. 1052-1053, as amended (21 U.S.C. 355)) and under authority delegated to him (21 CFR 5.82), finds that, on the basis of new information before him about each of these drug products, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effect it purports or is represented to have under the conditions of use prescribed.

These procedures are primarily intended to expedite media access to FDA public proceedings, including formal evidentiary hearings conducted pursuant to Part 12 of the agency's regulations. Under this guideline, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including the testimony of witnesses in the proceeding. Accordingly, the parties and nonparty participants to this hearing, and all other interested persons, are directed to the guideline, as well as the Federal Register notice announcing issuance of the guideline, for a more complete explanation of the guideline's effect on this hearing.

Therefore, under the Federal Food, Drug, and Cosmetic Act (section 505, 52 Stat. 1052 as amended (21 U.S.C. 355)), and under authority delegated to me (21 CFR 5.10), I order that a public hearing be held on the issues set out in this notice.

Dated: September 7, 1984.

Mark Novitch,

Deputy Commissioner of Food and Drugs.

[FR Doc. 84-24578 Filed 9-14-84; 8:45 am]

BILLING CODE 4180-01-M

[Docket No. 79N-0113; DESI 2847]

**Drugs for Human Use; Drug, Efficacy Study Implementation; Parenteral Multivitamin Products; Revocation of Exemption ("Paragraph XIV/Category 11"); Announcement of Effective Formulations; Followup Notice and Opportunity for Hearing**

**AGENCY:** Food and Drug Administration.  
**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) revokes the temporary exemption for certain parenteral multivitamin drug products. The exemption has permitted the drug products to remain on the market beyond the time limit scheduled for implementation of the Drug Efficacy Study. The agency also announces those parenteral multivitamin formulations that are effective and the conditions under which they may be marketed. In addition, this notice classifies other formulations as lacking substantial evidence of effectiveness, proposes to withdraw approval of those parts of new drug applications that provide for these formulations, and offers an opportunity for a hearing on the proposal.

**DATE:** Revocation of exemption effective September 17, 1984.

supplements to conditionally approved new drug applications due on or before November 18, 1984; hearing requests due on or before October 17, 1984; data in support of hearing requests due on or before November 18, 1984.

**ADDRESS:** Communications in response to this notice should be identified with Docket No. 79N-0113 (DESI 2847), directed to the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, except requests for opinion of applicability are to be sent to the address listed below.

Supplements to the conditionally approved new drug applications (identify with NDA number): Division of Endocrine and Metabolic Drug Products (HFN-810), Rm. 14B-05, Center for Drugs and Biologics.

Original abbreviated new drug applications: Division of Generic Drug Monographs (HFN-230), Center for Drugs and Biologics.

Request for hearing, supporting data, and other comments: Dockets Management Branch (HFA-305), Rm. 4-62.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFN-310), Rm. 218, Center for Drugs and Biologics, 5640 Nicholson Lane, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Nicholas P. Reuter, Center for Drugs and Biologics (HFN-368), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

#### Background

In a notice published in the Federal Register of July 27, 1972 (37 FR 15027), FDA announced its evaluations of reports received from the National Academy of Sciences/National Research Council, Drug Efficacy Study Group, on certain parenteral multivitamin drug products. The agency stated that the products, as then formulated, lacked substantial evidence of effectiveness for their claimed indications. This conclusion was not based upon any lack of effectiveness for the individual vitamins in the formulations, but because the available formulations lacked certain essential vitamins, or contained too much or too little of other vitamins, or both.

In a followup notice published in the Federal Register of December 14, 1972 (37 FR 28623), parenteral multivitamin products were granted a temporary exemption from the time limits imposed for the implementation of the Drug Efficacy Study. The temporary exemption was based on the recognized

critical medical importance of parenteral multivitamin therapy and the lack of alternative drugs. The exemption allowed the products to remain on the market as then formulated, while complex technical and medical problems were resolved and final formulations were developed and tested.

To facilitate the determination and evaluation of rational multivitamin formulations, FDA accepted the assistance offered by the American Medical Association (AMA). In December 1975, the AMA submitted its "Guidelines for Multivitamin Preparations for Parenteral Use," which recommended specific amounts of individual vitamins as well as detailed procedures for evaluating the stability, safety, and effectiveness of the formulations.

The AMA report stressed that the guideline formulations were estimated from the existing Recommended Daily Allowance (RDA), which in turn is based on dietary population surveys. The assumptions, applied by the AMA to correlate the established dietary allowances of the essential vitamins to the parenteral administration of vitamins to patients in various disease states, required that clinical trials be conducted to evaluate the guideline formulations.

FDA accepted the AMA guidelines with minor reservations and subsequently in a Federal Register notice published July 13, 1979 (44 FR 40933) amended the terms of the December 1972 temporary exemption to require conditional approval of a new drug application or a supplemental new drug application within specific time frames as a condition for the continued marketing of a parenteral multivitamin drug product. The agency granted conditional approval of applications based on the following criteria: (1) reformation in accord with the AMA guidelines as to the number and quantities of vitamins in the formulation; (2) an outline of studies to evaluate the stability and biological availability of the reformulated preparations, along the lines set forth in the AMA report; and (3) a plan or protocol for clinical effectiveness studies, also in accord with the AMA guidelines. The reformulated products could be marketed in place of the previous formulations after agency review and "conditional" approval of the submissions. This procedure allowed continued marketing of parenteral multivitamins while clinical testing and evaluation of the AMA guidelines formulations were carried out.

**Conditionally Approved Products (AMA Guideline Formulations)**

The products listed below have received conditional approval under the terms of the July 13, 1979 notice.

1. NDA 8-071; Berocca PN containing vitamin A (palmitate) 3,300 International Units (I.U.)/vial, vitamin D (ergocalciferol) 200 U.S.P. units/milliliter (mL), vitamin E (dl-alpha tocopherol) 10 U.S.P. units/mL, vitamin C (ascorbic acid) 100 milligrams (mg)/mL, folic acid 400 micrograms (mcg)/mL, niacin (niacinamide) 40 mg/mL, vitamin B<sub>2</sub> (riboflavin 5'-phosphate sodium) 3.8 mg/mL, vitamin B<sub>1</sub> (thiamine hydrochloride) 3 mg/mL, vitamin B<sub>6</sub> (pyridoxine hydrochloride) 4 mg/mL, vitamin B<sub>12</sub> (cyanocobalamin) 5 mcg/mL, pantothenic acid (dexpantenol) 15 mg/mL, and d-biotin 60 mcg/mL; Roche Laboratories, Division of Hoffmann-La Roche Inc., Roche Park, Nutley, NJ 07110.

2. NDA 8-071; Berocca-WS containing vitamin C (ascorbic acid) 100 mg/mL, folic acid 400 mcg/mL, niacin (niacinamide) 40 mg/mL, vitamin B<sub>2</sub> (riboflavin 5'-phosphate sodium) 3.8 mg/mL, vitamin B<sub>1</sub> (thiamine hydrochloride) 3 mg/mL, vitamin B<sub>6</sub> (pyridoxine hydrochloride) 4.0 mg/mL, vitamin B<sub>12</sub> (cyanocobalamin) 5 mcg/mL, pantothenic acid (d-pantenol) 15 mg/mL, and d-biotin 60 mcg/mL; Roche Laboratories, Inc.

3. NDA 8-809; MVI-12 containing vitamin A (retinol) 3,300 I.U./vial, vitamin D (ergocalciferol) 200 I.U./vial, vitamin E (dl-alpha tocopherol acetate) 10 I.U./vial, vitamin C (ascorbic acid) 100 mg/vial, folic acid 400 mcg/vial, niacin (niacinamide) 40 mg/vial, vitamin B<sub>2</sub> (riboflavin 5'-phosphate sodium) 3.8 mg/vial, vitamin B<sub>1</sub> (thiamine hydrochloride) 3.0 mg/vial, vitamin B<sub>6</sub> (pyridoxine hydrochloride) 4.0 mg/vial, vitamin B<sub>12</sub> (cyanocobalamin) 5 mcg/vial, pantothenic acid (d-pantenol/alcohol) 15 mg/vial, biotin 60 mcg/vial; USV Laboratories Division, USV Pharmaceuticals, Tuckahoe, NY 10707.

4. NDA 18-223; Multivitamin Additive containing vitamin A 3,300 I.U./5 mL, vitamin D 200 I.U./5 mL, vitamin E 10 I.U./5 mL, vitamin C (ascorbic acid) 100 mg/5 mL, folic acid 400 mcg/5 mL, niacin (niacinamide) 40 mg/5 mL, vitamin B<sub>2</sub> (riboflavin 5'-phosphate sodium) 3.8 mg/5 mL, vitamin B<sub>1</sub> (thiamine hydrochloride) 3.0 mg/5 mL, vitamin B<sub>6</sub> (pyridoxine hydrochloride) 4.0 mg/5 mL, vitamin B<sub>12</sub> (cyanocobalamin) 5 mcg/5 mL, pantothenic acid (pantothenyl alcohol) 15 mg/5 mL, d-biotin 60 mcg/5 mL; Abbott Labs, North Chicago, IL 60064.

5. NDA 18-439; MVC Plus containing vitamin A (retinol) 3,300 I.U./10 mL, vitamin D (ergocalciferol) 200 I.U./10 mL, vitamin E (dl-alpha tocopherol acetate) 10 I.U./10 mL, vitamin C (ascorbic acid) 100 mg/10 mL, folic acid 400 mcg/10 mL, niacin (niacinamide) 40 mg/10 mL, vitamin B<sub>2</sub> (riboflavin 5'-phosphate sodium) 3.8 mg/10 mL, vitamin B<sub>1</sub> (thiamine hydrochloride) 3 mg/10 mL, vitamin B<sub>6</sub> (pyridoxine hydrochloride) 4 mg/10 mL, vitamin B<sub>12</sub> 5 mcg/10 mL, pantothenic acid (dexpantenol) 15 mg/10 mL, biotin 60 mcg/10 mL; Ascot Hospital Pharmaceuticals, Inc., Skokie, IL 60076.

6. NDA 18-440; M.V.C. 9+3 containing vitamin A (retinol) 3,300 I.U./5 mL, vitamin D (ergocalciferol) 200 I.U./5 mL, vitamin E (dl-alpha tocopherol acetate) 10 I.U./5 mL, vitamin C (ascorbic acid) 100 mg/5 mL, folic acid 400 mcg/5 mL, niacin (niacinamide) 40.0 mg/5 mL, vitamin B<sub>2</sub> (riboflavin-5'-phosphate) 3.8 mg/5 mL, vitamin B<sub>1</sub> (thiamine hydrochloride) 3.0 mg/5 mL, vitamin B<sub>6</sub> (pyridoxine hydrochloride) 4.0 mg/5 mL, vitamin B<sub>12</sub> (cyanocobalamin) 5 mcg/5 mL, pantothenic acid (dexpantenol) 15.0 mg/5 mL, and biotin 60 mcg/5 mL; Lypho Med. Inc., Chicago, IL 60651.

7. NDA 18-920; M.V.I. Pediatric (lyophilized) each vial containing vitamin A (retinol) 2,300 U.S.P. units/vial, vitamin D (ergocalciferol) 400 U.S.P. units/vial, vitamin E (dl-alpha tocopherol acetate) 7 U.S.P. units/vial, vitamin C (ascorbic acid) 80 mg/vial, folic acid 140 mcg/vial, niacin (niacinamide) 17.0 mg/vial, vitamin B<sub>2</sub> (riboflavin-5'-phosphate sodium) 1.4 mg/vial, vitamin B<sub>1</sub> (thiamine hydrochloride) 1.2 mg/vial, vitamin B<sub>6</sub> (pyridoxine hydrochloride) 1.0 mg/vial, vitamin B<sub>12</sub> (cyanocobalamin) 1 mcg/vial, dexpantenol (d-pantothenyl alcohol) 5.0 mg/vial, biotin 20 mcg/vial, vitamin K<sub>1</sub> (phytonadione) 200 mcg/vial; Armour Pharmaceutical Co., P.O. Box 511, Kankakee, IL 60901.

8. NDA 18-933; M.V.I.-12 Lyophilized each vial containing vitamin A (retinol) 3,300 U.S.P. units, vitamin D (ergocalciferol) 200 units, vitamin E (dl-alpha tocopherol acetate) 10 U.S.P. units, vitamin C (ascorbic acid) 100 mg, folic acid 400 mcg, niacin (niacinamide) 40 mg, vitamin B<sub>2</sub> (riboflavin-5'-phosphate sodium) 3.8 mg, vitamin B<sub>1</sub> (thiamine) 3.0 mg, vitamin B<sub>6</sub> (pyridoxine) 4.0 mg, vitamin B<sub>12</sub> (cyanocobalamin) 5 mcg, dexpantenol (d-pantothenyl alcohol) 15.0 mg, biotin 60 mcg; Armour Pharmaceutical Co.

The Director of the Center for Drugs and Biologics has considered the results from the clinical trials on the recommended AMA formulations, and other available material, and has

determined that except for the pediatric parenteral formulation, the 1975 AMA guideline formulations are effective multivitamin preparations. However, the Director recognizes that as these products are used and evaluated in an ever increasing number of patients with a variety of disease conditions, future adjustments to the formulations may be necessary.

The temporary exemption announced in the December 14, 1972 notice as it pertains to any drug product of composition given above is hereby revoked. The drugs listed above are regarded as new drugs (21 U.S.C. 321(p)). A fully approved new drug application is now required for marketing them (except for M.V.I. Pediatric, as explained below). A supplemental new drug application is required for the products listed above (except for M.V.I. Pediatric) to revise their labeling to update the previous "conditionally approved" new drug applications providing for them.

In light of recent events involving reports of adverse effects associated with the use of a particular single entity parenteral vitamin E product in premature and low-birth-weight infants, the Director has determined that further evaluation of pediatric parenteral multivitamin formulations which contain vitamin E is required. (At the current time, it is unknown whether the adverse effects associated with the single entity product are related to the relatively large dosage of vitamin E administered, to the solubilizer in the product formulation, or to some other factor.) A future Federal Register notice will address the agency's conclusions on these products. Until that time, pediatric multivitamin products may be marketed only under the terms and conditions of the July 13, 1979 Federal Register notice (41 FR 40933).

**Products Lacking Substantial Evidence of Effectiveness**

The three products listed below were included in the initial DESI notice of July 27, 1972 (37 FR 15027). The sponsors of these products provided for a reformulated preparation in accord with the AMA guidelines as stated in the July 13, 1979 notice (44 FR 40933), and received conditional approval. Under the terms of that notice, the original products could remain on the market pending evaluation of the AMA guideline formulations. Insofar as the guideline formulations have now been found to be effective, the original formulations are now classified as lacking substantial evidence of effectiveness, their paragraph XIV

exemption is hereby revoked, and the Director proposes to withdraw approval of the following parts of the new drug applications, that provide for them:

1. NDA 8-071; those parts that provide for Berocca C and Berocca C-500 Injectable both containing thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, dexpanthenol, d-biotin, and ascorbic acid; Roche Laboratories, Inc.

2. NDA 8-809; those parts that provide for M.V.I. Injectable containing ascorbic acid, vitamin A, ergocalciferol, thiamine hydrochloride, riboflavin, niacinamide, pyridoxine hydrochloride, dexpanthenol, and dl-alpha tocopherol acetate; USV Pharmaceuticals.

In addition to the holder of the new drug applications named above, this notice applies to any person who manufactures or distributes a drug product that is not the subject of an approved new drug application and that is identical to a drug product named above. It may also be applicable, under 21 CFR 310.8, to a related or similar drug product that is not the subject of an approved new drug application. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product that the person manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of Drug Labeling Compliance (address given above).

#### Conditions for Approval and Continued Marketing of Formulations Evaluated as Effective

FDA has reviewed all available evidence and concludes that the parenteral multivitamin drug products formulated as listed below are effective for the applicable indication listed in the labeling conditions below.

**Conditions for Approval and Marketing.** FDA is prepared to approve abbreviated new drug applications and supplements to the conditionally approved new drug applications listed above (except for M.V.I. Pediatric) under conditions described herein.

##### 1. Form of drug.

(a) **Intravenous Multivitamin Preparations.** The preparation is an aqueous solution or lyophilized powder suitable for reconstitution and/or secondary dilution prior to intravenous infusion, and contains the specified amounts of the following individual vitamins, either as the moiety listed below or as the chemically equivalent salt or ester.

(i) **Adult formulation** (intended for ages 11 and older)

Ingredient	Amount per unit dose
Fat soluble vitamins	
A (retinol).....	3300 I.U.
D (ergocalciferol or cholecalciferol).....	200 I.U.
E (alpha-tocopherol).....	10 I.U.
Water soluble vitamins	
C (ascorbic acid).....	100 mg.
Folic acid.....	400 mcg.
Niacin.....	40 mg.
B <sub>1</sub> (thiamine).....	38 mg.
B <sub>2</sub> (riboflavin).....	3.0 mg.
B <sub>6</sub> (pyridoxine).....	4.0 mg.
B <sub>12</sub> (cyanocobalamin).....	5.0 mcg.
Pantothenic acid.....	15.0 mg.
Biotin.....	60.0 mcg.

(b) **Intramuscular Multivitamin Preparations.** The preparation is a sterile solution suitable for intramuscular injection.

(i) **Adult formulation.** The vitamin composition of the adult intramuscular formulation shall be that of the adult preparation (listed above) without the fat soluble vitamins.

##### 2. Labeling Conditions.

(a) The label bears the statement "Caution: Federal Law prohibits dispensing without prescription."

(b) The drug is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The indication is as follows:

##### (i) **Intravenous Multivitamin Preparations**

(a) **Adult.** This formulation is indicated as daily multivitamin maintenance dosage for adults and children age 11 and above receiving parenteral nutrition. It is also indicated in other situations where administration by the intravenous route is required. Such situations include surgery, excessive burns, fractures and other trauma, severe infectious diseases, and comatose states, which may provoke a "stress" situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients.

The physician should not await the development of clinical signs of vitamin deficiency before initiating vitamin therapy. The use of a multivitamin product obviates the need to speculate on the status of individual vitamin nutriture.

This product (administered in intravenous fluids under proper dilution) contributes intake of these necessary vitamins, except vitamin K, toward maintaining the body's normal resistance and repair processes.

Patients with multiple vitamin deficiencies or with markedly increased requirements may be given multiples of the daily dose for 10 or more days as indicated by the clinical situation. This product does not contain vitamin K, which may have to be administered separately. Clinical testing indicates that some patients do not maintain adequate levels of certain vitamins when this formulation in recommended amounts is the sole source of vitamins. No vitamin deficiencies were clinically evident, but blood levels of vitamin A, C, D, and folic acid

declined in a number of subjects who received this formulation as the only vitamin source for 4 to 6 months. Therefore, in patients for whom total parenteral nutrition will be continued for long periods of time, these vitamins should be monitored. If deficiencies appear to be developing, multiples of the formulation (1.5 to 3 times) may be needed for a period of time. When multiples of the formulation are used for more than a few weeks, vitamins A and D should be monitored occasionally to be certain that an excess accumulation of these vitamins is not occurring.

##### (ii) **Intramuscular Multivitamin Preparations.**

(a) **Adult.** This product is indicated for adults and children 11 years of age or older for conditions in which (1) intake or absorption of the water-soluble vitamins is inadequate and oral intake must be supplemented; or (2) there is a known or suspected serious depletion of the water-soluble vitamins and immediate treatment by the intramuscular route is advisable.

Conditions which may require parenteral administration of water-soluble vitamins may include disorders which can affect oral intake, gastrointestinal absorption, or utilization, such as: comatose states, persistent vomiting, prolonged fever, severe infectious diseases, major surgery, extensive burns, fractures and other traumas, chronic alcoholism, diarrhea, achlorhydria, or liver disease.

The physician should not await the development of clinical signs of vitamin deficiency before initiating therapy as there are few specific or pathognomonic signs of early vitamin deficiencies.

(c) **CONTRAINDICATIONS:** Known hypersensitivity to any of the vitamins in this product or a pre-existing hypervitaminosis.

3. **Marketing Status.** (a) Marketing of the drug products that are now the subjects of conditionally approved new drug applications (except for M.V.I. Pediatric) may be continued provided that on or before November 18, 1984 the holder of the application submits (i) a supplement for revised labeling as needed to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted, and (ii) a supplement to provide updating information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)). FDA will evaluate the submitted material and, if adequate, will grant full approval to the conditionally approved new drug applications.

(b) Approval of an abbreviated new drug application (21 CFR 314.2) containing full information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities,

and controls) of new drug application form FD-356H (21 CFR 314.1(c)) must be obtained before marketing such products. The bioavailability regulations (21 CFR 320.21) require any person submitting a full or abbreviated new drug application after July 7, 1977, to include either evidence demonstrating the in vivo bioavailability of the formulation or information to permit waiver of the requirement. The bioavailability requirements are waived under 21 CFR 320.22(b)(1) for intravenous products formulated described in this notice (see section 1(a) *Form of Drug*). Marketing the drug products before approval of a new drug application will subject the products, and those persons who caused the products to be marketed, to regulatory action.

(c) Marketing of M.V.I. Pediatric may be continued under the terms and conditions of the July 13, 1979 Federal Register notice (41 FR 40933).

#### Notice of Opportunity for Hearing

On the basis of all the data and information available to him, the Director of the Center for Drugs and Biologics is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5) and 300.50, and demonstrating the effectiveness of the parenteral multivitamin formulations listed above under "*Products Lacking Substantial Evidence of Effectiveness.*"

Therefore, notice is given to the holders of the new drug applications and to all other interested persons, that the Director of the Center for Drugs and Biologics proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of those parts of the new drug applications and all amendments and supplements thereto providing for the formulations classified as lacking substantial evidence of effectiveness on the ground that new information before him with respect to the drug products, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence that these formulations will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling. If no hearing is requested, then those parts of the new drug applications

that pertain to the formulations evaluated as lacking substantial evidence of effectiveness (part of NDA 8-071 providing for Berocca C and Berocca C-500; part of NDA 8-809 providing for M.V.I. Injectable) will be considered withdrawn and no further order will issue.

This notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, or for any other reason.

In accordance with section 505 of the act (21 U.S.C. 355) and the regulations promulgated under it (21 CFR Parts 310 and 314), the applicants and all other persons who manufacture or distribute a drug product that is identical, related, or similar to the drug products named above (21 CFR 310.6), and not the subject of an approved new drug application, are hereby given an opportunity for a hearing to show why approval of those parts of the new drug applications providing for the formulations evaluated as lacking substantial evidence of effectiveness should not be withdrawn, and an opportunity to raise, for administrative determination, all issues relating to the legal status of the drug products named above and of all identical, related, or similar drug products not the subject of an approved new drug application.

The applicant or any other person subject to this notice under 21 CFR 310.6 who decide to seek a hearing, shall file (1) on or before December 17, 1984 a written notice of appearance and request for hearing, and (2) on or before November 16, 1984 the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a granting

or denial of a hearing are contained in 21 CFR 314.200.

The failure of the applicants or any other person subject to this notice under 21 CFR 310.6 to file a timely written notice of appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by the person not to make use of the opportunity for a hearing concerning the action proposed, and a waiver of any contentions concerning the legal status of the relevant drug product. Any such drug product, the composition of which has been evaluated in this notice as lacking substantial evidence of effectiveness, may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such a drug product from the market. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the affected parts of the applications, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions pursuant to this notice are to be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-1053 as amended (21 U.S.C. 352, 355)), and under the authority delegated to the Director of the Center for Drugs and Biologics (21 CFR 5.70 and 5.82).

Dated: September 12, 1984.

Harry M. Meyer, Jr.,

Director, Center for Drugs and Biologics.

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