CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-265

CORRESPONDENCE

MAY - 3 2000

NDA 21-265

AIRMAIL

Sabex, Inc.
Attention: Ms. Leonor Ferreira
Director, Regulatory Affairs
145, Jules-Leger Street
Boucherville, Quebec
CANADA J4B 7K8

Dear Ms. Ferreira:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Multi-12/K_1 Pediatric (multiple vitamins for infusion)

Therapeutic Classification: Standard (S)

Date of Application: April 20, 2000

Date of Receipt: April 21, 2000

Our Reference Number: NDA 21-265

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 20, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 21, 2001, and the secondary user fee goal date will be April 21, 2001.

Our regulations require that a U.S. agent be designated for official communications between the Agency and non-U.S. applicants. Please submit, as an amendment to this NDA, a new form FDA 356h with the name and address of the U.S. agent.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosage regimens are required to contain an assessment of the safety and effectiveness of the product in pediatrics patients unless this requirement is waived or deferred (*63 FR 66632*). We note that you have fulfilled the pediatric study requirement at this time.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

/S/

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-265
HFD-510/Div. Files
HFD-510/S.McCort
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: ddk/April 28, 2000
Initialed by: Galliers 5.1.00
final: ddk/May 1, 2000

ACKNOWLEDGEMENT (AC)

SABEX®

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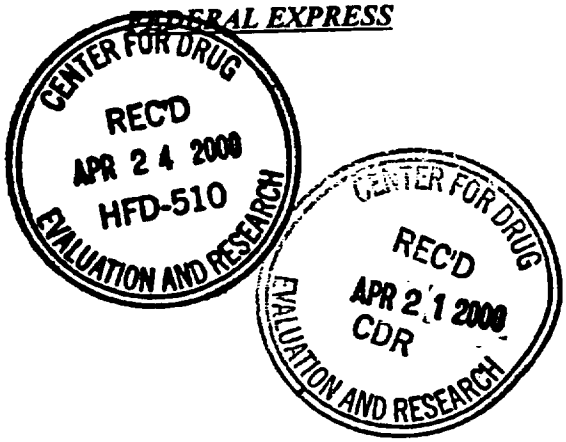
April 20th, 2000

FEDERAL EXPRESS



U.S. Food and Drug Administration
Central Document Room
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolic & Endocrine Drug Products
12229 Wilkins Avenue
Rockville, Maryland
USA 20852

RE: NDA Submission for Multi-12®/K_1 Pediatric (Multiple Vitamins for Infusion)

Dear Sir or Madam:

SABEX INC. hereby submits an original new drug application ("NDA") seeking approval to market **Multi-12®/K_1 Pediatric**, an injectable preparation of multiple vitamins for infusion in pediatric patients. This product is formulated in accordance with the Federal Register notice of January 26th, 2000 (65 CFR 4253). This submission is being submitted as a 505(b)(2) application further to our discussions with the FDA during our Pre-NDA Meeting, the meeting minutes of which are included in the section titled Previous Correspondence. Furthermore, since a large portion of the information pertinent to this application has been reviewed in the application for the adult formulation, Multi-12 (NDA 21-163), it was agreed between Sabex and the FDA that, to eliminate redundancy, all information that has been reviewed in NDA 21-163 would be referenced to said application. New information peretinent specifically to the enclosed formulation is hereby included.

This NDA consists of 7 volumes. SABEX is filing an archival copy (in blue folders) of the NDA with all the information required as well as five technical review copies each in their respective coloured jackets as dictated by the guidelines and each containing the information pertinent to that particular review, in accordance with the guidelines.

Each volume is paginated separately on the right hand corner, including volume and page number. Each review contains the application index and is preceded by a sectional index for that particular technical section. The sectional index is not paginated and also includes a list of the appendices included in that review copy. Each subsection of the application, including appendices, is separated with tabs labelled with the title or abbreviation thereof, for that subsection. A field copy (burgundy folders) containing a true complete copy of the CMC and Microbiology technical sections, as well as the first volume, of this NDA is also included.

.../2

REQUEST FOR EXPEDITED REVIEW: A formal request for expedited review is hereby made for this application based. Our request is based on the current ongoing shortage situation that the United States has faced since late 1996 for the only marketed product available in the US, MVI Pediatric, which received conditional approval in 1983 (as of today's date final approval for this product has not been granted by FDA). A strict allocation program is in place that rations the drug, which is a standard part of clinical therapy, to only the smallest of newborns. All other pediatric patients must use the adult formulation, which is formulated with propylene glycol and excess polysorbates, in the case MVI-12, and which is indicated for children 11 years and older. In support of our request we have enclosed the most recent ASPEN notice as well as a recent letter to the FDA by ASPEN, dealing specifically with this situation. We trust that based on the current situation, and in the best interests of clinical and patient stakeholders, that this application will be granted expedited review, in order to alleviate the current situation as soon as possible.

Please direct any written communications regarding this NDA to the following contact person at SABEX INC. or by phone to the listed number:

Ms. Leonor Ferreira, M.Sc., MBA
Director, Regulatory Affairs
SABEX INC.
145 Jules-Leger Street
Boucherville, (QC), CANADA J4B 7K8

Phone: (450) 641-4903 ext. 2161
FAX: (450) 641-6408

e-mail: l.ferreira@sabex-inc.com

ASPEN
American society for Parenteral & enteral nutrition

☐ LETTER ☐ N.A.I. ☐ MEMO

C&J INITIALS DATE

We trust that the enclosed application is satisfactory.

Sincerely,

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

encl.

ORIGINAL

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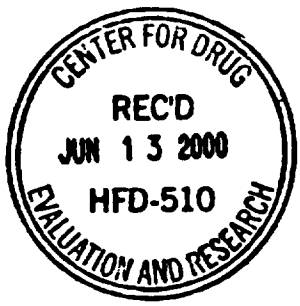
NEW CORRESP

Purolator

June 5, 2000

John K. Jenkins, M.D.
Acting Director, Division of Metabolic & Endocrine Drug Products
DMEDP, HFD-510
Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland
USA 20857



Re: Amendment to NDA 21-265

Dear Dr. Jenkins:

Please find enclosed our "Notification of US Agent" letter that we forget to include in our original submission. As a consequence, form 356h has been corrected to include the information on our US agent. A new form 356h duly completed and signed is hereby enclosed. As there were no changes to the Attachments to form 356h these are not being resubmitted. The disclaimer "to the best of knowledge" has been removed from our debarment certification and a new document duly signed is also included.

We have also noted that there were inadvertent errors in the drug product specifications and stabilty protocols submitted. These have been corrected and are herein submitted.

We trust that all is satisfactory. Should you have any queries do not hesitate to contact the undersigned.

Sincerely,

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

REVIEWS COMPLETED -

OSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

OSO INITIALS DATE

4/28/00

encl.

SABEX INC
145 Jules-Leger
Tel: 450-641-4303

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ORIGINAL

Federal Express

November 2, 2000

David G. Orloff, M.D.
Director, Division of Metabolic & Endocrine Drug Products
DMEDP, HFD-510
Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland
USA 20857

Re: Amendment to NDA 21-265

took out time for expiration date

Dear Dr. Orloff:

Please find enclosed an amendment to NDA 21-265 of Multi-12/K Pediatric. This amendment includes updated stability data in support of a —month expiration period as well as validation and forced degradation studies for two alternate analytical methods. A desk copy of this package has been forwarded to Mr. Steve McCort, Project Manager.

We trust that all is satisfactory. Should you have any queries or comments do not hesitate to contact the undersigned.

Sincerely,

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO
CSO INITIALS
DATE

encl.

c.c.: Mr. Steve McCort, Project Manager, Endocrinology and Metabolism (FDA)

SABEX® Pharmaceutical Products
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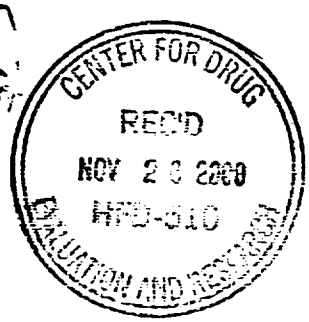
Federal Express

N-000 - BZ

November 27, 2000



David G. Orloff, M.D.
Director, Division of Metabolic & Endocrine Drug Products
DMEDP, HFD-510
Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland
USA 20857

ORIGINAL

Re: AMENDMENT - NDA 21-265

Dear Dr. Orloff:

Please find enclosed an Amendment to NDA 21-265 of Multi-12/K Pediatric. This amendment is being submitted in accordance with the Federal Register Final Rule on "Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition" issued January 26, 2000 (65FR4103) and effective January 26, 2001. A copy of this Final Rule is enclosed.

By this rule FDA has amended its regulations to add certain labelling requirements for aluminum content in small volume parenterals used in total parenteral nutrition. By virtue of this ruling, the labelling of Multi-12/K Pedaitric (NDA 21-265) is being changed to comply with said ruling.

In addition, this ruling requires applicants to submit to FDA validated assay methods for determining aluminum content in parenteral drug products.

This amendment includes a complete report of the validated assay methods used to determine the aluminum content of Multi-12/K Pediatric, including data on 3 batches. Also included are copies of the draft labelling wherein are the labelling changes made to the inner (immediate container) labels. These changes are highlighted for ease of review and no other changes have been made to the originally submitted labelling.

NDA 21,265

.../2

This amendment includes the original archival copy as well as a Chemistry Review copy. A copy of the labelling is also enclosed for the review of said documents. A desk copy of this package has been forwarded to Mr. Steve McCort, Project Manager.

We trust that all is satisfactory. Should you have any queries or comments do not hesitate to contact the undersigned.

Sincerely,

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

encl.

c.c.: Mr. Steve McCort, Project Manager, Endocrinology and Metabolism (FDA)

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November 30, 2000

ORIGINAL

ORIG AMENDMENT

Polysorbate 80 concentra
are within those used
in approved products, as
per inactive ingredient
Guide. This issue
was addressed by
Drs Temeck and
Davis-Bruno in
the medical +
pharmacology
reviews of
the NDA.
NAI

/S/
2/8/01

Jean Jemeck, MD
Endocrinology and Metabolism (FDS)
DMEDP, HFD-510
Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland
USA 20857

RE: **NDA 21-265: References cited in Polysorbate 80 Toxicology Report**

Dear Dr. Jemeck:

Please find enclosed all the references cited in the Polysorbate 80 Toxicology Report submitted as part of NDA 21-265.

Please note that some of the references listed in said report were cited in the enclosed references and therefore a copy of the original citation is not enclosed. However, should you need the original citations, please do not hesitate to communicate with us. It will be our pleasure to retrieve these if they are available.

We trust that the enclosed is satisfactory. Should you have any questions or comments, do not hesitate to contact the undersigned.

Sincerely,

Leonor Ferreira, M.Sc., M.B.A.
Director, Regulatory Affairs

LF/hg

SABEX INC
145 Jules-Leger

SABEX®

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Federal Express

January 9, 2001

NEW CORRESP

David G. Orloff, M.D.
Director, Division of Metabolic & Endocrine Drug Products
DMEDP, HFD-510
Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland
USA 20857

ORIGINAL

Re: AMENDMENT - NDA 21-265

Dear Dr. Orloff:

Please find enclosed an Amendment to NDA 21-265 of Multi-12/K Pediatric.

This amendment is simply to modify the commercial batch size range proposed for the afore-mentioned product given that we failed to originally ask for a maximum — — as permitted and suported by the data provided. Therefore we propose the following.

	Original Proposal	Primary Batch sizes Submitted	Current Proposal
Vial 1	—		
Vial 2	—		

Further increases in the batch size shall be requested post-approval via a supplement as required.

We trust that this is satisfactory. Should you have any questions or comments do not hesitate to contact the undersigned.

Sincerely,

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

cc.: *Dr. David Lewis, Chemistry Reviewer, Endocrinology and Metabolism (FDA)*

SABEX INC
145 Jules-Leger Tel: 450-641-4903

MESSAGE CONFIRMATION

02/09/01 11:34
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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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FOOD AND DRUG ADMINISTRATION
DIVISIONS OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: **February 9, 2001**

TO:

Name: **David** 3/20626854

Fax No: 31206168543

Phone No: 01131206212223

Location: Amsterdam Hotel

FROM:

Name: **Steve McCort**
Project Manager

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

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BL

February 13, 2001

David G. Orloff, M.D.
Director, Division of Metabolic & Endocrine Drug Products
DMEDP, HFD-510
Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland
USA 20857

Re: AMENDMENT - NDA 21-265 – INFUVITE *Pediatric*
Final Label Revisions

Dear Dr. Orloff:

Please find enclosed in the form of an Amendment to our NDA 21-265 revised labelling statements included in our package insert as agreed upon between ourselves and Dr. Jean Temeck in our telephone conversation of today's date. We have included hard copies of both annotated as well as final copies of the package insert. Also included is a diskette containing the electronic versions of said labelling.

We trust that this is satisfactory. Should you have any questions or comments do not hesitate to contact the undersigned.

Sincerely,

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

cc.: *Steve McCort, Project Manager, Endocrinology and Metabolism (FDA)*
submitted by fax 2001-02-13

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

SABEX INC
145 Jules-Léger
Boucherville, QC, Canada
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Tel : 450-641-4903
Fax : 514-596-1460

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Federal Express

February 12, 2001

David G. Orloff, M.D.
Director, Division of Metabolic & Endocrine Drug Products
DMEDP, HFD-510
Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland
USA 20857

Re: AMENDMENT - NDA 21-265 – INFUVITE *Pediatric*
Complete Response to Labelling Recommendations

Dear Dr. Orloff:

Please find enclosed in the form of an Amendment to our NDA 21-265 a complete response to the labelling recommendations made by FDA, dated February 9, 2001, a copy of which is enclosed. We hereby confirm that the name of the product shall be henceforth known as **INFUVITE *Pediatric*.** This change has been made on all labelling. Changes to the name on specifications, etc., will be made internally.

All labelling recommendations have been agreed to and have been incorporated as suggested by FDA. We have included hard copies of both annotated as well as final copies of inner and outer labels as well as the package insert. Also included is a diskette containing the electronic versions of said labelling.

In addition, please find enclosed a duly completed and signed Financial Disclosure Certification (FDA Form 3454), whereby Sabex Inc. certifies that no investigator used in conduct of studies used in the support of NDA 21-265 were subject to any financial arrangement that may impair the objectivity of the study.

You shall also find enclosed a copy of the Stability Protocol submitted by Fax on January 25, 2001, to Dr. David Lewis further to is request.

We trust that this is satisfactory. Should you have any questions or comments do not hesitate to contact the undersigned.

Sincerely,

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

cc.: *Steve McCort, Project Manager, Endocrinology and Metabolism (FDA)*

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

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Fax : 514-596-1460