CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-163

ADMINISTRATIVE DOCUMENTS

SABEX®

Pharmaceutical Products
Produits pharmaceutiques

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 **Multi-12®**, submitted pursuant to section 505(b)(2).

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

SABEX INC.

Suzanne Levesque, B.Pharm., MBA
Vice-President, Scientific Affairs

June 25/1999
Date

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

Tel : 450-641-4903
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Exclusivity Checklist

NDA: 20-163				
Trade Name: Multi-12®				
Generic Name: Multiple Vitamins for Infusion				
Applicant Name: Sabex Inc.				
Division: DMEDP (HFD-510)				
Project Manager: Steve McCort				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes		No	X
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
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:				
Explanation:				
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?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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?	Yes	X	No	
If yes, NDA # 8-809				
Drug Name: M.V.I-12® (Multi-Vitamins for Infusion)				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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 (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.	Yes		No	
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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
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 <u>any one</u> 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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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.				

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 BLOCKS.**				
Basis for conclusion:				
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:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				

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:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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 #1				
Investigation #2				
Investigation #3				
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	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
If yes, explain:				

/S/

Signature of PM

5-5-00

Date:

/S/

Signature of Division or Office Director

5-19-00

Date:

cc:
Original NDA
HFD-510/Division File
HFD-93/Mary Ann Holovac
HFD-104/TCrescenzi

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21163	**Trade Name:**	MULTI-12 (MULTIPLE VITAMINS/INFUSION)
Supplement Number:		**Generic Name:**	MULTI-12 (MULTIPLE VITAMINS/INFUSION)
Supplement Type:		**Dosage Form:**	FIJ Injection
Regulatory Action:	AP	**Proposed Indication:**	Indicated as a daily multivitamin maintenance supplement for adults and children 11 and older receiving parenteral nutrition or inother situations in which adminstration by intravenous route is required.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO. Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) __X__Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The labeling for this NDA has been approved. SMM/May 18, 2000

This NDA is only applicable for 11 years and up. The Sponsor has submitted a separate new NDA 21-165 for the pediatric population below 11 years and is formulated in accordance with the September 17, 1984 Federal Register Notice, "Drugs for Human Use: Parenteral MultivitamiProducts:Drug Efficacy Study Implementation." A seperate Federal Register notice dated January 20. 2000,"Pediatric Parenteral Multivitmin Products" specifies a different formulation for chileren younger than 11 years. Parenteral products as described in these FR notices do not require pediatric studies. Therefore, the pediatric study requirement is waived for this application.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, STEPHEN MCCORT

/S/ — Signature

5-18-00 — Date

SABEX®

Pharmaceutical Products
Produits pharmaceutiques

DEBARMENT CERTIFICATION

Sabex Inc. hereby certifies that it has not and will not use in any capacity the services of any person debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act, in connection with this application. In addition, Sabex Inc. states that neither Sabex 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.

Sabex Inc.

Suzanne Levesque
Vice President
Quality Assurance & Regulatory Affairs

2000/05/09
Date

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NDA: 21,163
Drug: Multi-12
Sponsor: Sabex Inc.

Date submitted: 7/19/99
Date received: 7/20/99
Date reviewed: 4/5/2000

Drug: Multi-12
Indication: Daily multivitamin maintenance supplement for adults and children aged 11 years and older receiving parenteral nutrition.
Route of administration: intravenous
Marketing history: received marketing approval from Canada in 1994 (based on published literature; no clinical studies were performed by the sponsor); also marketed in Peru, Saudi Arabia, Venezuela, Singapore and Macau. It was imported into the U.S. from Canada from 4/97-6/99 to alleviate the U.S. parenteral multivitamin shortage.
Formulation: The table below compares Sabex Multi-12 formulation to Astra's MVI-12 which is currently marketed in the U.S. (note: both products contain 2 vials of 5 ml each):

Vial 1:

	MVI-12 (Astra)	Multi-12 (Sabex)
Vitamin A	3,300 IU	3,300 IU
Vitamin D	200 IU	200 IU
Vitamin E	10 IU	10 IU
Vitamin C	100 mg	100 mg
Vitamin B1 (Thiamin)	3 mg	3 mg
Vitamin B2 (Riboflavin)	3.6 mg	3.6 mg
Vitamin B6 (Pyridoxine)	4 mg	4 mg
Niacinamide	40 mg	40 mg
Dexpanthenol	15 mg	15 mg
Polysorbate 80	1.6 %	1.4%
Polysorbate 20	0.028%	Nil
Propylene glycol	1.5 g (30%)	Nil
Gentistic acid ethanolamide	2%	Nil
Butylated hydroxytoluene	0.002%	Nil
Butylated hydroxyanisole	0.0005%	Nil
Sodium hydroxide	To adjust pH	To adjust pH
Water for injection	q.s. 5 ml	q.s. 5 ml

Vial 2:

	MVI-12 (Astra)	Multi-12 (Sabex)
Biotin	60 ug	60 ug
Folic acid	400 ug	400 ug
Vitamin B12 (Cyanocobalamin)	5 ug	5 ug
Propylene glycol	30%	30%
Citric acid and sodium citrate	To adjust pH	To adjust pH
Sodium hydroxide	To adjust pH	Nil
Water for injection	q.s. 5 ml	q.s. 5 ml

Both products are formulated according to the AMA's guideline for parenteral multivitamin products (J Parenteral and Enteral Nutrition 3(4):258-262, 1975). The guideline states that even if a product is formulated according to the guidelines, clinical testing should be carried out to ensure appropriate maintenance of vitamin concentrations. The July 13, 1979 Federal Register Notice provides guidance to sponsors regarding the conduct of these clinical studies.

As the above table demonstrates, the active ingredient (i.e. vitamin) composition of Sabex's Multi-12 is identical to Astra's MVI-12 which is currently marketed in the U.S. and is designated in the Orange Book as the reference listed drug. In a September 15, 1998 pre-NDA meeting with the sponsor, the sponsor asked the Division of Metabolism and Endocrine Drug Products (DMEDP) if clinical studies could be waived and the Division responded in the affirmative.

Moreover, the prescribing information for Multi-12: indications for use and dosage and administration, are the same as for MVI-12. Hence, the Sabex product does appear to qualify as a 505(j) application according to the Federal Food, Drug and Cosmetic Act, section 505, pages 87-88 and 94. However in a September 15, 1998 meeting, Sabex communicated to DMEDP that their application was deemed ineligible as a 505(j) by the Office of Generic Drugs due to differences in the inactive ingredient composition. However, as the above table indicates, all the inactive ingredients in the Sabex product are also contained in the Astra product in equal or smaller quantities.

Background:

Sabex provided background information on multivitamins, which can be found in any standard textbook including their physiological functions, pharmacokinetics and clinical manifestations of deficiencies and excesses. In addition, 7 articles from the published literature, including the AMA guidance, were submitted to provide a general overview on major topics related to total parenteral nutrition and vitamin status assessment. General principles rather than the specifics of these individual studies will be presented here because individual vitamin requirements vary with many factors. It is known that the amount of vitamins necessary to maintain adequate blood levels varies with the patient's age, nutritional status, presence of concomitant illness/fever, concomitant use of parenteral nutrient solutions (pH and bisulfite concentration affect the stability of some vitamins) and use of concomitant drugs (drug-vitamin interactions). However, more precise information is needed in many of these areas. In addition, differences in timing and methods of sample collections and assays used to measure the vitamin levels, affect study results. Also, plasma/serum concentrations of vitamins may not necessarily reflect tissue stores. Since there are significant body stores of the fat-soluble vitamins (A, D, E and K), inadequate replacement may not be evident for many months. Furthermore, the clinical significance of depressed blood levels of certain vitamins during trauma and infection has not been clearly defined. Finally, the stability of vitamins may be affected by exposure to light, temperature extremes, the amount of time they are in the infusate bottle/bag, etc. Therefore, although the formulation recommended by the AMA should be appropriate for the majority of patients, it is necessary to monitor the vitamin status of individual patients, particularly if the formulation is the only source of vitamins for months-years.

The FDA will be issuing a Federal Register Notice (FRN) requiring sponsors of adult parenteral multivitamin preparations to modify their formulations based on the outcome of a public workshop sponsored by the FDA's DMEDP and the AMA's Division of Personal and Public Health Policy on August 21, 1985. At this workshop: "Multivitamin Preparations for Parenteral Use", it was recommended that the dosage of vitamins B1, B6, C and folic acid be increased and vitamin K added based on review of additional data including that obtained from clinical testing of the 1975 AMA formulation. The specific changes per unit dose are delineated below:

Vitamin	1975 AMA Formulation	Updated AMA Formulation
Vitamin K	None	150 ug
Vitamin C	100 mg	200 mg
Folic acid	400 ug	600 ug
Vitamin B1 (thiamin)	3.0 mg	6.0 mg
Vitamin B6 (pyridoxine)	4.0 mg	6.0 mg

On Tuesday, April 4, 2000, Dr. David Orloff, Mr. Steve McCort and myself, had a t-con with Mr. David Read and Ms. Catchings, Regulatory Policy, to discuss when this FRN will be published and the impact it will have on our regulatory action for the Sabex product. Mr. Read informed us that HFD-510 can issue an approval letter to Sabex for Multi-12 if the letter is issued prior to the pending FRN. If our regulatory action letter is not issued until after the FRN is published, and this is expected to occur by next week, then Sabex would be required to reformulate their product as the current formulation would no longer be deemed safe and effective.

Adverse Reactions:

Per Sabex, no reports of adverse events have been received from either Canada or the U.S. However, due to the similarities between the Sabex and Astra multivitamin products, Sabex will be required to modify their proposed Adverse Reactions section of the package insert to reflect ADR's received by FDA from Astra. Please refer to FDA's December 1, 1995 letter to Astra requesting them to add shortness of breath and lip edema to their PI. Also, a report was received from MedWatch on 2/7/2000 of a 28 yr. old M who experienced hives and bronchoconstriction during MVI-12 administration.

In addition, FDA has received rare reports of anaphylactic reactions reported with Multi-12 administration (#'s 01-000324, 912875A0649, 913448A0730, 920887A0187 and 930256A0084).

Drug-vitamin interactions:

A number of interactions between vitamins and drugs have been reported which may affect their metabolism. Appropriate references for vitamin-drug interactions should be consulted for specific listings. In addition to those listed in the label for both Astra's MVI-12 and Sabex's draft label for Multi-12, the following drug-vitamin interactions may occur:

1. Folic acid may lower the serum concentration of phenytoin and phenobarbital resulting in increased seizure frequency[1, 2 and 5]. Conversely, phenytoin may decrease serum folic acid concentrations

and, therefore, should be avoided in pregnancy[1] . Folic acid may decrease the patient's response to methotrexate therapy[3].

2. Pyridoxine may decrease the efficacy of levodopa by increasing its metabolism[1 and 2] . Concomitant administration of hydralazine or isoniazid may increase pyridoxine requirements[1, 2 and 5] .
3. In patients with pernicious anemia, the hematologic response to vitamin B12 therapy may be inhibited by concomitant administration of chloramphenicol[2] .
4. Several vitamins have been reported to decrease the activity of certain antibiotics. Thiamin, riboflavin, pyridoxine, niacinamide and ascorbic acid have been reported to decrease the antibiotic activity of erythromycin, kanamycin, streptomycin, oxycycline and lincomycin[6] Bleomycin is inactivated in vitro by ascorbic acid and riboflavin[7]
5. Vitamin K may antagonize the hypoprothrombinemic effect of oral anticoagulants[2 and 5].

References:

1. DrugDex Evaluations
2. Drug Interactions and Updates Quarterly, Hansten and Horn, editors; Lea and Febiger, Malvern, Pa; Applied Therapeutics, Inc., Vancouver, Washington, 1990.
3. Drug Facts and Comparisons, Steven Hebel, ed.; Facts and Comparisons, Inc., St. Louis, Mo., 1999.
4. Friedrich W, Vitamins, Walter de Gruyter, Berlin and New York, 1988.
5. Goodman and Gilman, The Pharmacological Basis of Therapeutics, 9th edition.
6. Trissel LA. Handbook on Injectable Drugs, 8th ed. American Society of Hospital Pharmacists, 1994.
7. AHFS 96 Drug Information; McEvoy GK, ed. American Society of Health-System Pharmacists, Bethesda, MD, 1996.

Drug-Laboratory Test Interactions:

Ascorbic acid in the urine may cause false negative urine glucose determinations[1 and 2].

No exogenous vitamin C should be ingested for 48-72 hours before amine -dependent stool occult blood tests are conducted because possible false negative results may occur[1 and 2].

1. Drug Facts and Comparisons, Steven Hebel, ed.; Facts and Comparisons, Inc., St. Louis, Mo., 1999.
2. Clinical Guide to Parenteral Micronutrition, T Baumgartner, ed.; Educational Publications, Ltd., Melrose Park, Illinois, 1984.

Multi-12 Labeling Comments (note: the following labeling comments are written based on the addition of vitamin K which will be required pending publication of the FRN):

Indications and Usage section:

"Aqueous" multiple vitamin preparation for intravenous infusion:
Multi-12® (Multiple Vitamins for Infusion) makes available a combination of important oil-soluble and water-soluble vitamins in an aqueous solution, formulated for incorporation into intravenous solutions. The liposoluble vitamins A, D and E have been solubilized in an aqueous medium with polysorbate 80, permitting intravenous administration of these vitamins.

INDICATIONS AND USAGE

Multi-12® is indicated as a daily multivitamin maintenance supplement for adults and children aged 11 and older receiving parenteral nutrition.

Multi-12® is also indicated in other situations where administration by the intravenous route 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.

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

Multi-12® (administered in intravenous fluids under proper dilution) contributes intake of 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 dosage for two or more days, as indicated by the clinical status.

Multi-12® does not contain vitamin K which may have to be administered separately.

Some patients do not maintain adequate levels of certain vitamins when a multiple vitamin preparation, such as **Multi-12®**, in recommended amounts, is the sole source of vitamins. Blood levels of vitamins A, C, D and folic acid may decline in patients receiving parenteral multivitamins as their sole source of vitamins for 4 to 6 months. Therefore, in patients for whom total parenteral nutrition will be continued for long periods of time blood vitamin concentrations should be monitored to ensure maintenance of adequate levels. 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.

Last paragraph:

Sentence 2: replace "...for long periods of time" with: "...for 4 to 6 months."

Sentence 3: refers only to vitamins A, C, D and folic acid. Replace "...these vitamins should be monitored" with: "...blood vitamin concentrations should be monitored to ensure maintenance of adequate levels."

Contraindications section:

Change "...sensitivity..." to "...hypersensitivity..." and add: "...or excipients..." after the word "vitamins".

Add the following sentence: "Allergic reactions have been known to occur following intravenous administration of thiamin 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."

Precautions section:

Begin this section with the following:

"If this formulation is the only source of vitamins for long periods of time, blood concentration of each of the vitamins should be monitored, particularly vitamins A, C, D and folic acid, to determine if deficiencies are occurring. If deficiencies are developing or when long-standing vitamin deficiencies are present, it may be necessary to add therapeutic amounts of certain vitamins to supplement the maintenance vitamins provided in Multi-12."

Rename the Drug Interactions subsection, Drug-Drug/Solution Interactions and begin this subsection with the following bolded sentence:

"Caution should be exercised when administering multivitamin formulations containing vitamin K to patients on anticoagulant therapy. In such patients, vitamin K may antagonize the hypoprothrombinemic response to anticoagulant drugs, such as warfarin and its congeners. Therefore, periodic monitoring of prothrombin/INR response is essential in determining the appropriate dosage of anticoagulant therapy."

The remainder of this subsection should be rewritten as follows:

Multi-12 (Multivitamins for Infusion) is not physically compatible with alkaline solutions or moderately alkaline drugs such as Diamox (Acetozolamide), Diuril Intravenous Sodium (Chlorthiazide sodium), Aminophlline or sodium bicarbonate. Achromycin (tetracycline HCl) may not be physically compatible with Multi-12. Also, it has been reported that folic acid is unstable in the presence of calcium salts such as calcium gluconate. Direct addition of Multi-12 to intravenous fat emulsions is not recommended. Consult appropriate references for listings of physical compatibility of solutions and drugs with the vitamin infusion. In such circumstances, admixture or Y-site administration with vitamin solutions should be avoided.

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

Folic acid may lower the serum concentration of phenytoin

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

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

In patients with pernicious anemia, the hematologic response to vitamin B12 therapy may be inhibited by concomitant administration of chloramphenicol.

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

Vitamin K may antagonize the hypoprothrombinemic effect of oral anticoagulants (see bolded statement above).

Consult appropriate references for additional specific vitamin-drug interactions.

Some of the vitamins in Multi-12 may react with vitamin K bisulfite or sodium bisulfite; if bisulfite solutions are necessary, patients should be monitored for vitamin A and thiamin deficiencies."

After the Drug-Drug/Solution Interactions subsection, add the following:

Drug-Laboratory Test Interactions:

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

No exogenous vitamin C should be ingested for 48-72 hours before amine-dependent stool occult blood tests are conducted because possible false negative results may occur."

Allergic Reactions section:

Revise the first paragraph to read:

"There have been rare reports of anaphylactic reactions following parenteral multivitamin administration. Rare reports of anaphylactoid reactions have also been reported following large intravenous doses of thiamin. However, the risk of an allergic reaction is negligible if thiamin is co-administered with other vitamins in the B group."

Under "Allergic", add: shortness of breath, wheezing and lip edema.

Overdosage section:

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

Evaluation and Regulatory Action:

The active ingredients in Multi-12 are identical to MVI-12 which is designated in the Orange Book as the reference listed drug. Differences in the inactive ingredients between the two products are minor and clinically insignificant. Both formulations comply with the 1975 AMA guidance for parenteral multivitamin drug products. Therefore, the application should be approved.

However, based on the outcome of a 1985 workshop jointly sponsored by the FDA and the AMA, the expert consensus was to increase the amounts of vitamins B1, B6, C and folic acid and to add vitamin K to adult parenteral multivitamin products. A FRN specifying these changes has been drafted. Once this FRN is published, which is imminent, manufacturers will be required to reformulate their product so that it will be deemed safe and effective by the FDA. Therefore, if the regulatory action letter is issued after this FRN is published, a non-approvable letter will need to be issued to Sabex.

In addition, the above labeling comments should be communicated to Sabex. Given the similarities between Sabex's Multi-12 and Astra's MVI-12, the labeling for these two products should be identical. Comments not contained in the MVI-12 label should be conveyed to Astra.

/S/

Jean Temeck, M.D.

cc. NDA Arch 21,163
NDA Division file
cc. HFD-510: Dr. Ahn and Mr. McCort

/S/

4-11-00

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA #_21-163_____ Drug _ MULTI-12® (Multivitamis for Infusion)_____

Applicant_Sabex Inc._____ CSO McCort_____/Phone 827-6415____

User Fee Goal Date:__May 20, 2000_____

Arrange package in the following order: ___Check or Comment_____

1. ACTION LETTER with supervisory signatures — AP__x___AE_____ NA_____
   Are there any Phase 4 commitments? — Yes_____ No__x_____
2. Have all disciplines completed their reviews? — Yes____x_____ No_____
   If no, what review(s) is/are still pending? _____
3. Completed copy of this CHECKLIST in package — Chem/Ther Types___5S___
4. LABELING (package insert and carton and container labels). — Draft_____
   (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.) — Revised Draft____x_____ Final_____
5. PATENT INFORMATION ____x_____
6. EXCLUSIVITY CHECKLIST ____x_____
7. PEDIATRIC PAGE ____x_____
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). x____
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES _____NA_____
   If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
   If no audits were requested, include a memo expaining why.
10. REVIEWS:

DIVISION DIRECTOR'S MEMO	If more than 1 review for any	_____
GROUP LEADER'S MEMO	1 discipline, separate reviews	_____
MEDICAL REVIEW	with a sheet of colored paper.	____x_____
SAFETY UPDATE REVIEW	Any conflicts between reviews	____NA_____
STATISTICAL REVIEW	must have resolution documented	____NA_____
BIOPHARMACEUTICS REVIEW		____x_____
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		____x_____
Statistical Review of Carcinogenicity Study(ies)		____NA_____
CAC Report/Minutes		____NA_____
CHEMISTRY REVIEW		____x_____
Labeling and Nomenclature Committee Review Memorandum		____x_____
Date EER completed _5-4-2000_____ (attach signed form or CIRTS printout)		OK__x____ No____
FUR needed __NA_____ FUR requested __NA_____		
Have the methods been validated?		Yes (attach)_____ No___x__
Environmental Assessment Review / FONSI		Review _____ FONSI____x__
MICROBIOLOGY REVIEW		_____x_____
What is the status of the monograph?		_____NA_____

11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes _____x_____
12. MINUTES OF MEETINGS _____x_____
    Date of End-of-Phase 2 Meeting ___NA_____
    Date of pre-NDA Meeting _9-16-98_____
13. ADVISORY COMMITTEE MEETING MINUTES — Minutes_____ Info Alert_____
    or, if not available, 48-Hour Info Alert or pertinent section of transcript. — Transcript_____ No mtg___x__
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS _____x_____
15. If approval letter, has ADVERTISING MATERIAL been reviewed? — Yes_____ No____x____
    If no and this is an AP with draft labeling letter, has advertising matenal already been requested? — Yes, documentation attached_____ No, included in AP ltr _____

revision 3/7/96

CONTINUE TO NEXT PAGE ☞

16. INTEGRATED SUMMARY OF EFFECTIVENESS _____x_____

17.	INTEGRATED SUMMARY OF SAFETY	x

revision: 3/7/96

FOOD AND DRUG ADMINISTRATION
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: **May 18, 2000**

TO:

Name: **Leonor Ferreira**

Fax No: 450-641-6408

Phone No: 450-641-4903

Location: SABEX

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

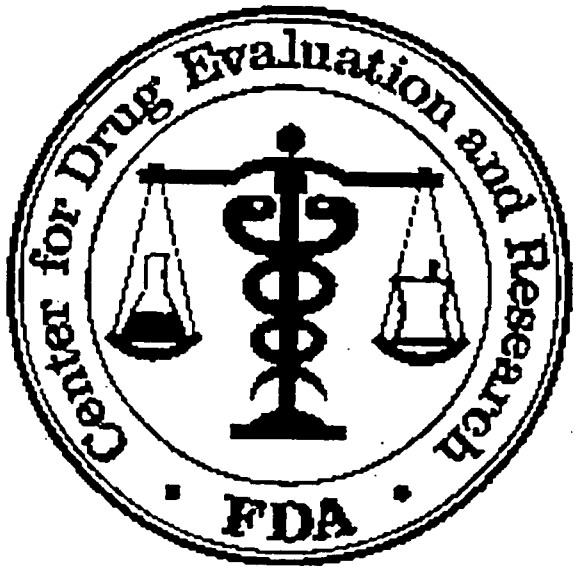
Location: FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

Comments:

Approval letter for NDA 21-163; Multi-12 (Multiple Vitamins for Infusion)

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: May 18., 2000



TO:

Name: **Ilze Antons**

Fax No: 617-374-7470

Phone No: 617-374-7425

Location: Genzyme

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

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

Comments:

Comments from May 17, 2000 meeting with FDA.

(FAX) - BL

SABEX® Pharmaceutical Products
Produits pharmaceutiques

FACSIMILE TRANSMITTAL

DATE	*2000-05-16*
ATTENTION	*Mr. Steve McCort* *Project Manager, Division of Metabolic & Endocrine Drug Products*
ADDRESSEE	*FDA, Rockville, Maryland, USA*
FACSIMILE #	*(301) 443-9282*
FROM	*Ms. Leonor Ferreira* *Tel: (450) 641-4903, ext. 2161*
NUMBER OF PAGES (INCLUDING THIS COVER PAGE): 22 *If all pages are not received, please call the SENDER at the above-mentioned number.*	

Re: Response to Labelling Revision Request - NDA 21-163

Dear Mr. McCort,

The present is a response to the labeling recommendations received from FDA dated May 16, 2000, and pertaining to our labeling submitted May 10, 2000.

We have addressed these recommendations as follows:
To the **Description** section of the Package Insert: The sentences have been modified to read "contains" instead of "provides" as per FDA's recommendations.

To the **INDICATIONS AND USAGE** section of the Package Insert: The second sentence of the third paragraph has been deleted as per FDA's recommendations.

To the **OVERDOSAGE** section of the Package Insert: The typographical error in the hypervitaminosis in line 3 has been corrected.

To the **PRECAUTIONS** section of the Package insert, in the subsection pertaining to **Nursing Mothers**: The following sentence was added as per FDA's recommendation: "It is not known whether this drug is excreted in human milk. However, because many drugs are excreted in human milk, caution should be exercised when Multi-12 is administered to a nursing mother." Please note that the word "However" has been added at the begining of the second sentence this does not change the meaning of the statement, it is **grammatical change only**, so that the sentence does not start with the word "because". I trust this is acceptable.

.../2

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

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

To the **Dosage and Administration** section of the Package insert:

1. In paragraph 3 the sentence "Discard any unused portion" has been added. Further to a phone conversation between us and FDA, via yourself, it was agreed that this statement is more appropriate than "Discard any portion in the unused vials".
2. The first sentence of Paragraph 5 has been modified in accordance with the FDA recommendations. The second sentence remains intact as confirmed with FDA.

To the **Draft Inner Labels**, for both Vials 1 and 2:
Under the established name the statement "For intravenous infusion after dilution " has been modified to include the term "only", thus maintaining consistence with the outer label as well as with the package insert.

Enclosed are both annotated and final clean non-annotated copies of the labels and package insert (see footnotes for versions). In the annotated copies deletions have been striked out and additions, other than those proposed, have been highlighted. The non-annoated versions are clean final versions with all strike outs and highlights removed and are representative of the final label. Electronic copies have been submitted by e-mail as requested.

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

Best regards,

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

Division of Metabolic and Endocrine Drug Products, HFD-510

CONSUMER SAFETY OFFICER REVIEW

Application Number: 21-163

Name of Drug: Multi-12® (Multiple Vitamins for Infusion)

Sponsor: Sabex Inc.

Material Reviewed

Submission Date: May 16, 2000
Receipt Date: May 16, 2000 (Fax)

Background and Summary Description: The Sponsor submitted draft labeling in their original NDA 21-163 dated July 19, 1999. FDA FAXED a copy of labeling comments/proposed revisions to the firm on May 8, 2000. The Firm responded with a May 10, 2000 draft labeling to the FDA request by FAX. The FDA sent a FAX of the May 10, 2000 label labeling recommendations to the Firm on May 16, 2000. After discussions with the firm per t/con (May 16. 2000) the firm FAXed a revised label to FAXED a revised label (with a hard copy to follow) which included the changes requested by FDA and additional changes agreed upon per the May 16. 2000. telephone conversation between Leonor Ferreira, Sabex and Steve McCort, FDA.

Review

The revised draft labeling dated May 16, 2000, FAXED to FDA, was compared with the previous May 10. 2000 label and the draft July 19, 1999 labeling.

All changes requested from the May 16, 2000, FAX from were agreed upon in the May 16, 2000, telephone conversation with additional changes between Leonor Ferreira of Sabex and Steve McCort of FDA as follows:

PACKAGE INSERT

The **DESCRIPTION** section, The sentences have been modified to read *"contain"* instead of *"provides"* as per FDA recommendation.

To the **INDICATIONS AND USAGE** section the second sentence which reads "*The use of a multivitamin product obviates the need to speculate on the status of individual vitamin nutriture.*" has been deleted per FDA recommendation

To the **OVERDOSAGE** section the typographical error in the *hypervitaminosis* has been corrected per FDA recommendation.

To the **PRECAUTIONS** section, the following sentence was added to the Nursing Mothers, per FDA recommendation, except for the word, *"However"* added at the beginning of the second sentence *"It is not known whether this drug is excreted in human milk. However, because many drugs are excreted in human milk, caution should be exercised when Multi-12 is administered to a nursing mother.* The Sponsor added the word "However" as a grammatical change only to the sccond sentence. This change is acceptable to the FDA reviewing staff.

To the **DOSAGE AND ADMINISTRATION** section, the following changes are noted:

In Paragraph 3, The recommendation *"Discard any portion in the unused vials,"* has been modified to read *"Discard any unused portion"*. The new language has been agreed upon after discussions with Dr. Duu-Gong Wu, Chemistry Team Leader, FDA.

The first sentence of Paragraph 5 which reads "*"After Multi-12® is diluted in an intravenous infusion, the resulting solution should be refrigerated unless it is to be used immediately. The solution should be used within 24 hours after dilution."* has been added per FDA recommendation. The second sentence which reads *"Some of the vitamins in this product, particularly A, D and riboflavin, are light sensitive, therefore, exposure to light should be minimized.,"* has been retained per consultation with Dr. Duu-Gong Wu, Chemistry Team Leader, FDA

DRAFT OUTER AND INNER LABELS:

To the Draft Inner Labels, The word *"only"* has been added under the established name to now read *"For intravenous infusion after dilution only."* Per FDA recommendation.

This change is consistent with the wording on the Package Insert, the Inner Labels and the Outer Labels, which includes the same wording.

Conclusions

The draft labeling dated May 16, 2000, includes all the labeling changes requested or agreed upon by the Firm and FDA. With the concurrence of the reviewing staff the May 16, 2000 draft labeling, for NDA 21-163, Multi-12® (Multiple Vitamins for Infusion) is approvable.

/S/

Jean Temeck, M.D.
Medical Reviewer
~~Medical Reviewer~~

/S/

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

/S/

Ron Steigerwalt, PhD.
Pharmacology Team Leader

/S/

Steve McCort
Project Manager

/S/

David Orloff, M.D.
Medical Team Leader
~~Chemistry Reviewer~~

/S/

David Lewis, Ph.D.
Chemistry Reviewer

/S/

Robert Shore, PharmD
Biopharm. Reviewer

/S/

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

cc:
HFD-510/Div. Files
HFD-510/SMcCort

CSO REVIEW

cc: NDA 21-163
HFD-510/Div File
HFD-510/SMcCort

MEMORANDUM

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

DATE: May 10, 2000

FROM: Steve McCort
Project Manager

SUBJECT: Labeling for NDA 21-163; Multi-12

TO: File for NDA 21-163

The firm has submitted an amendment dated May 10, 2000 (Fax with hard copy to follow in response to the Division's labeling recommendations) dated May 8, 2000 for NDA 21-163, Multi-12 ((Multiple Vitamins for Infusion).

The package submitted includes the following:
1. A cover letter that responds to the Divisions labeling recommendations.
2. A copy of the firm's revised annotated labeling (and clean copy with annotation) dated May 10. 2000.
3. A copy of the July 19, 1999 labeling
4. A copy of the May 8, 2000 labeling comments Faxed to the firm.

Please review both the revised labeling and cover letter with specific comments. If you agree with all of the changes made in the labeling please sign and concur below. If not, give review comments and attach to memo.
Thanks.

/S/
Steve McCort
Project Manager, HFD-510

/S/
Ron Steigerwalt, Ph.D.
Pharmacology Reviewer

/S/
Hae Young Ahn, Ph.D.
Biopharm Team Leader

/S/
Jean Temeck, M.D.
Medical Reviewer

CONCURRENCE:

/S/
David Lewis, Ph.D.
Chemistry Reviewer

/S/
Robert Shore, Pharm D.

/S/
Duu-Gong Wu, Ph.D.
Chem. Team Leader

/S/
David Orloff, M.D.
Deputy Director

The terminology should be consistant between the container label and P.I. (contains vs provides — should all state contains) RBL 5-10-00

-overdosage section typo.

Recommendations to Sponsor to the May 10, 2000 revised draft labeling:

To the **DESCRIPTION** section:

The sentence that reads:

"Each 5 mL of Vial 1 provides", should be changed to read.

"Each 5 mL of Vial 1 contains,"

The sentence that reads,

"Each 5 mL of Vial 2 provides," should be changed to read,

"Each 5 mL of Vial 2 contains,"

To the **INDICATIONS AND USAGE** section:

Delete the second sentence in the third paragraph: *"The Use of a multivitamin product obviates the need to speculate on the status of individual vitamin nutriture."*

To the **OVERDOSAGE** section, line 3 which reads,

"hypeervitaminosis,"

change to read
"hypervitaminosis"

To the **PRECAUTIONS** section, **Nursing Mothers**, section, add the following as a last sentence.

"It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Multi-12 is administered to a nursing mother."

To the **DOSAGE AND ADMINISTRATION** section:

1. Paragraph 3, add the sentence, **"Discard any portion in the unused vials."**

2. Paragraph 5 should be revised to read as follows:

"After Multi-12® is diluted in an intravenous infusion, the resulting solution should be refrigerated unless it is to be used immediately. The solution should be used within 24 hours after dilution."

To the **Draft Outer Inner Label, MULTI-12® VIAL 1**, and for the Draft Outer Label **Multi-12® Vial 2:**

Under the established name, **MULTI-12®**,and under **Vial 1**

"For intravenous infusion after dilution,"

should be changed to read,

"For intravenous infusion only"

OK for FAX:

_____

David Orloff, M.D.
Deputy Director. HFD-510

SABEX®
Pharmaceutical Products
Produits pharmaceutiques

Purolator

May 10, 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 in Response to Labelling Revision Request - NDA 21-163

Dear Dr. Jenkins:

The present is a response to the labeling recommendations received from FDA dated May 8, 2000, a copy of which is hereby enclosed. We have addressed these recommendations as follows:

All comments on pages 1-3 have been adopted and the appropriate revisions made with the noted exception of the cautionary statement in bold-face type. We have prefaced this statement by adding that **Multi-12®** is not formulated with vitamin K followed by the cautionary statement in bold-face type as suggested. We believe that this will clarify any potential confusion in the event that the statement may erroneously lead the health care practitioner to believe that this formulation contains vitamin K, this is even more important now that reformulations to add vitamin K are forthcoming in the near future.

Typographical errors noted in your recommendations have been corrected.

Pertaining to the following recommendations we have addressed them as follows:

A. PACKAGING:

We do not feel that the term [redacted] is appropriate to define our product as that may suggest a drug device combination. Furthermore, the US reference product MVI-12, on which the labeling is based, does not carry the term [redacted]

.../2

SABEX INC
145 Jules-Leger
Boucherville, QC Canada
J4B 7K8
Tel : 450-641-4903
Fax . 514-596-1460

In addition, this type of product is not new to the US market, this format has been in use since at least the early 1980's.

Lastly, it is for this reason that we have chosen to use different coloured caps for Vials 1 and 2 (grey and red). Upon opening the carton 5 grey-capped vials and 5 red-capped vials are found (or one of each in the 2-vial set), thus sending a message that there are 2 different vials. From our experience in Canada and for the two years we were importing this product under special import consideration to the United States (1997-1999) we have never received reports of medication errors as a result of inability to distinguish the vials. Thus we wish to pursue the opportunity to market both the product packaged in single-dose sets and 5 dose sets as presented to the FDA.

acceptable

B. CONTAINER LABEL

This dosage form, although available in the United States since the 1980's, is not a compendial product and no other similar product is listed in the official compendium. However, this generic form of the name is derived from what is used by MVI-12, "multi-vitamin infusion". The name has been modified to read "for infusion" for the simple purpose of indicating that it is not a product ready *to be infused* but must be further prepared *for infusion*. This is consistent with the compendia's nomenclature for products that are defined as "Injection" or "for Injection". The "for" infers that the products in question are to be used to prepare injections or, in our case, infusions. Based on this we feel that the generic name is consistent with recent nomenclature trends by the USP, although not an officially recognized name.

Furthermore, the "oil- and water-soluble vitamins injection" name is not appropriate as this refers particularly to an old product Berocca C ——— which could be given by intramuscular injection directly, therefore the term injection, the use of this name would be potentially dangerous as it would infer that this product is a ready-to-use injection. Thus we propose to retain the name as is.

acceptable 5-10-00

Labeling in bold-face type indicating that the product must be diluted prior to use is available on both outer and inner labels. Clear directions as also found in the package insert. In addition we have modified the term "For intravenous infusion only" to read "For intravenous infusion after dilution only".

Points 2-6 have been adopted as suggested.

.../3

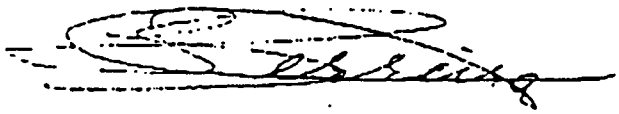
C. CARTON LABELING and PACKAGE INSERT LABELING

All points adopted.

Enclosed are both annotated and non-annotated copies of the labels and package insert (see footnotes for versions). In the annotated copies deletions have been striked out and additions, other than those proposed, have been highlighted. The non-annotated versions are clean final versions with all strike outs and highlighted regions removed and are representative of the final label. Electronic copies have been submitted by e-mail as requested.

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

encl.

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

Multi-12 Labeling Comments :

Indications and Usage section:

Last paragraph:

Sentence 2: replace "...for long periods of time" with: "...for 4 to 6 months."

Sentence 3: refers only to vitamins A, C, D and folic acid. Replace "...these vitamins should be monitored" with: "...blood vitamin concentrations should be monitored to ensure maintenance of adequate levels."

Contraindications section:

Change "...sensitivity..." to "...hypersensitivity..." and add: " . or excipients..." after the word "vitamins".

Add the following sentence: "Allergic reactions have been known to occur following intravenous administration of thiamin 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."

Precautions section:

Begin this section with the following:

"If this formulation is the only source of vitamins for long periods of time, blood concentration of each of the vitamins should be monitored, particularly vitamins A, C, D and folic acid, to determine if deficiencies are occurring. If deficiencies are developing or when long-standing vitamin deficiencies are present, it may be necessary to add therapeutic amounts of certain vitamins to supplement the maintenance vitamins provided in Multi-12."

Rename the Drug Interactions subsection, Drug-Drug/Solution Interactions and begin this subsection with the following bolded sentence:

"Caution should be exercised when administering multivitamin formulations containing vitamin K to patients on anticoagulant therapy. In such patients, vitamin K may antagonize the hypoprothrombinemic response to anticoagulant drugs, such as warfarin and its congeners. Therefore, periodic monitoring of prothrombin/INR response is essential in determining the appropriate dosage of anticoagulant therapy."

The remainder of this subsection should be rewritten as follows:

Multi-12 (Multivitamins for Infusion) is not physically compatible with alkaline solutions or moderately alkaline drugs such as Diamox (Acetozolamide), Diuril Intravenous Sodium (Chlorthiazide sodium), Aminophilline or sodium bicarbonate. Achromycin (tetracycline HCl) may not be physically compatible with Multi-12. Also, it has been reported that folic acid is unstable in the presence of calcium salts such as calcium gluconate. Direct addition of Multi-12 to intravenous fat emulsions is not recommended. Consult appropriate references for listings of physical compatibility of

We suggest that the established name be revised, based upon the USP/NF[1], *to* _____ *with appropriate labeling specifying that the product must be diluted.* Sponsors who market related products should also revise the name of this product accordingly.

2. In the designation of multivitamin content, *we recommend substitution of "mcg" or "micrograms" for the symbol "µg"*, as the Greek symbol is often mistaken for "mg", resulting in a 10-fold overdose.

3. We recommend revision of the statement *"For intravenous infusion only" to "Must be diluted"*.

4. *Revise the statement "Caution: Rx only. Federal law prohibits dispensing without prescription" to "Rx only"*, per the FDA Modernization Act of 1997.

5. Revise the statement "Each 5mL of Vial 1 [or 2] *provides:*" to "Each 5mL...*contains:*".

6. Delete statement "Consult package insert for dosage and full prescribing information" and *replace with "Usual dosage: See package insert."*

C. CARTON LABELING and PACKAGE INSERT LABELING

1. For clarity, on front panel, *revise the section entitled "Contents"* to "Contains 5 each of Vial 1 and Vial 2" or a related statement. The use of "5 x" does not convey a clear meaning. Similar use of the abbreviation appears under "How Supplied" in the package insert and should be revised.

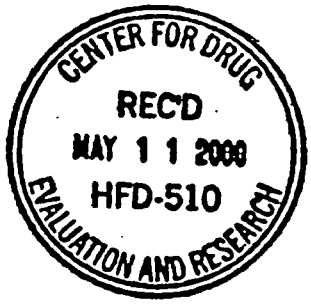
2. Under Dosage and Administration, for consistency with the carton label, *revise statement "Store between 2-8 [degrees] C (36-46 [degrees] F)"* to "Store under refrigeration between 2-8 [degrees] C (36-46 [degrees] F)".

this has been changed on the container label but not yet on the PI.

SABEX®

Pharmaceutical Products
Produits pharmaceutiques

PUROLATOR



May 09, 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 21-163 for Multi-12® (Multiple Vitamins for Infusion)**

Dear Dr. Jenkins:

The present is an amendment to our NDA 21-163 for the above-mentioned product currently under review. The enclosed is further to an information request received from the FDA on May 08, 2000, to reword our Debarment Certification. Therefore, please find enclosed a revised and duly signed Debarment Certification. This document was forwarded by fax on today's date to the attention of Mr. Steve McCort.

We trust that the above is satisfactory. Should you require additional information do not hesitate to contact the undersigned at (450) 641-4903 Ext. 2161.

Sincerely,

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

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

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

FOOD AND DRUG ADMINISTRATION
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: **May 8, 2000**

TO:		FROM:	
Name:	**Leonor Ferreira**	Name:	**Steve McCort**
Fax No:	450-641-6408	Fax No:	301-443-9282
Phone No:	450-641-4903	Phone No:	301-827-6415
Location:	SABEX	Location:	FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

Comments:

Labeling recommendations for NDA 21-163; Multi-12 (Multiple Vitamins for Infusion)

NDA 21-163 - MULTI-12 (MULTIPLE VITAMINS FOR INFUSION)

The following labeling comments are recommended for draft labeling submitted with the original application dated July 20, 1999. In addressing the labeling recommendations please submit the following by FAX:

1. A cover letter addressing the recommended labeling revisions.

2. A paper copy of the revised annotated labeling.

3. A copy of the revised labeling (clean copy of PI)

In addition please send an electronic version of the package insert labeling by E-Mail. My E-Mail address is:MCCORTS@CDER.FDA.GOV

Multi-12 Labeling Comments :

Indications and Usage section:

Last paragraph:

Sentence 2: replace "...for long periods of time" with: "...for 4 to 6 months."

Sentence 3: refers only to vitamins A, C, D and folic acid. Replace "...these vitamins should be monitored" with: "...blood vitamin concentrations should be monitored to ensure maintenance of adequate levels."

Contraindications section:

Change "...sensitivity..." to "...hypersensitivity..." and add: "...or excipients..." after the word "vitamins".

Add the following sentence: "Allergic reactions have been known to occur following intravenous administration of thiamin 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."

Precautions section:

Begin this section with the following:

"If this formulation is the only source of vitamins for long periods of time, blood concentration of each of the vitamins should be monitored, particularly vitamins A, C, D and folic acid, to determine if deficiencies are occurring. If deficiencies are developing or when long-standing vitamin deficiencies are present, it may be necessary to add therapeutic amounts of certain vitamins to supplement the maintenance vitamins provided in Multi-12."

Rename the Drug Interactions subsection, Drug-Drug/Solution Interactions and begin this subsection with the following bolded sentence:

"Caution should be exercised when administering multivitamin formulations containing vitamin K to patients on anticoagulant therapy. In such patients, vitamin K may antagonize the hypoprothrombinemic response to anticoagulant drugs, such as warfarin and its congeners. Therefore, periodic monitoring of prothrombin/INR response is essential in determining the appropriate dosage of anticoagulant therapy."

The remainder of this subsection should be rewritten as follows:

Multi-12 (Multivitamins for Infusion) is not physically compatible with alkaline solutions or moderately alkaline drugs such as Diamox (Acetozolamide), Diuril Intravenous Sodium (Chlorthiazide sodium), Aminophlline or sodium bicarbonate. Achromycin (tetracycline HCl) may not be physically compatible with Multi-12. Also, it has been reported that folic acid is unstable in the presence of calcium salts such as calcium gluconate. Direct addition of Multi-12 to intravenous fat emulsions is not recommended. Consult appropriate references for listings of physical compatibility of

solutions and drugs with the vitamin infusion. In such circumstances, admixture or Y-site administration with vitamin solutions should be avoided.

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

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

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

In patients with pernicious anemia, the hematologic response to vitamin B12 therapy may be inhibited by concomitant administration of chloramphenicol.

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

Vitamin K may antagonize the hypoprothrombinemic effect of oral anticoagulants (see bolded statement above).

Consult appropriate references for additional specific vitamin-drug interactions.

Some of the vitamins in Multi-12 may react with vitamin K bisulfite or sodium bisulfite; if bisulfite solutions are necessary, patients should be monitored for vitamin A and thiamin deficiencies."

After the Drug-Drug/Solution Interactions subsection, add the following:

Drug-Laboratory Test Interactions:

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

Allergic Reactions section:

Revise the first paragraph to read:

"There have been rare reports of anaphylactic reactions following parenteral multivitamin administration. Rare reports of anaphylactoid reactions have also been reported following large intravenous doses of thiamin. However, the risk of an allergic reaction is negligible if thiamin is co-administered with other vitamins in the B group."

Revise "Allergic", to read urticeria, shortness of breath, wheezing and angioedema.

Overdosage section:

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

Please add the following to the **Precautions** section of the package insert.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity, mutagenicity and fertility studies have not been performed with Multi-12® (Multiple Vitamins for Infusion).

Pregnancy:

Pregnancy Category C: Animal reproduction studies have not been conducted with Multi-12® (Multiple Vitamins for Infusion). Multi-12® (Multiple Vitamins for Infusion) should be given to a pregnant woman only if clearly needed. Pregnant women should follow the U.S. Recommended Daily Allowances for their condition, because their vitamin requirements may exceed those of nonpregnant women. The use of Multi-12® (Multiple Vitamins for Infusion) has not been studied in human pregnancy.

Additonal Labeling Revisions

Under **INDICATIONS AND USAGE:**

Paragraph 2, line 3, ". . . which make provoke . . "
Please replace the word "make" with the word "may."

Paragraph 4, line 2, ". . . Multi-12 (administered in intravenous fluids . . .vitamins, excpt viitamin K . . ."
Please correct the spelling of the word "exept" to "except."

Paragraph 7, line 1, "Some patients do not maintain adequate levels of certain viatmins . . . "
Please correct the spelling of the word "viatmins" to "vitamins."

In addition we have the following recommendations:

From a safety perspective, we have no objections to the use of the proprietary name "Multi-12". However we recommend that the term [redacted] be associated with the term [redacted] be associated with the tradename, e.g. "Multi-12™ [redacted] The established name of this product needs to be revised to comply with the USP/NF standards.

A. PACKAGING

1. Although it is necessary for reasons of chemical incompatibility among the vitamin components to have two separate vials to complete the 12-vitamin supplementation, based on previous experience with evaluation of medication errors, this type of packaging configuration is error-prone. *We suggest, therefore, that the sponsor add the word [redacted] to the product name, e.g. Multi-12™ [redacted]* This will provide an additional reminder to personnel using the product that each component individually does not comprise a complete dose.

2. *We would recommend that the product only be packaged in single cartons with 2 vials.* The firm's proposal to have a carton of 5's (5 vials of Vial 1 and 5 vials of Vial 2) unnecessarily increases the risk of personnel compounding a solution with 2 identical vials, resulting in the wrong dose being administered.

B. CONTAINER LABEL (single- and five-dose packages)

1. The established drug name chosen by the manufacturer for this product, "multiple vitamins for infusion" is a pharmaceutical dosage form that is not officially recognized by the United States Pharmacopeia in their official compendia. Including the phrase "for infusion" in the established drug name is also a safety concern in that the user may assume that the undiluted product is ready for infusion, the reverse of the likely intent of the manufacturer.

We suggest that the established name be revised, based upon the USP/NF[TM], to _____ *with appropriate labeling specifying that the product must be diluted.* Sponsors who market related products should also revise the name of this product accordingly.

2. In the designation of multivitamin content, *we recommend substitution of "mcg" or "micrograms" for the symbol "μg"*, as the Greek symbol is often mistaken for "mg", resulting in a 10-fold overdose.

3. We recommend revision of the statement *"For intravenous infusion only" to "Must be diluted".*

4. *Revise the statement "Caution: Rx only. Federal law prohibits dispensing without prescription" to "Rx only"*, per the FDA Modernization Act of 1997.

5. Revise the statement "Each 5mL of Vial 1 [or 2] *provides:*" to "Each 5mL...*contains:*".

6. Delete statement "Consult package insert for dosage and full prescribing information" and *replace with "Usual dosage: See package insert."*

C. CARTON LABELING and PACKAGE INSERT LABELING

1. For clarity, on front panel, *revise the section entitled "Contents"* to "Contains 5 each of Vial 1 and Vial 2" or a related statement. The use of "5 x" does not convey a clear meaning. Similar use of the abbreviation appears under "How Supplied" in the package insert and should be revised.

2. Under Dosage and Administration, for consistency with the carton label, *revise statement "Store between 2-8 [degrees] C (36-46 [degrees] F)"* to "Store under refrigeration between 2-8 [degrees] C (36-46 [degrees] F)".

MEMORANDUM

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

DATE: May 5, 2000

FROM: Steve McCort
Project Manager
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II, CDER

SUBJECT: Financial Disclosure Statement for NDA 21-163 Multi-12 (Multiple Vitamins for Infusion)

TO: File for NDA 21-163

The Financial Disclosure statement is not needed for NDA 21-163 since the application contains no covered studies. This 505(b)(2) application refers to NDA 8-809, which did not contain clinical studies but is based upon Federal Register Notice dated September 17, 1984, *"Drugs for Human Use; Efficacy Study Implementation; Parenteral Multivitamin Products; Revocation of Exemption ("Paragraph XIV/Category 11") Announcement of Effective Formulations; Followup Notice and Opportunity for Hearing."*

/S/
Steve McCort, HFD-510

MEMORANDUM OF MEETING MINUTES

Meeting Date: May 2, 2000
Time: 9:30 am
Location: PKLN 14B-56

Application: NDA 21-163

Drug: MULTI-12 (Multiple Vitamins for Infusion)

Type of Meeting: Team Meeting - Wrap-up meeting

Meeting Chair: John Jenkins, M.D. Acting Division Director

Meeting Recorder: Steve McCort, Project Manager

Attendees:

John Jenkins. M.D., Acting Division Director
David Orloff, M.D., Deputy Director
Jean Temeck, M.D., Medical Reviewer
Duu-Gong Wu. Ph.D., Chemistry Team Leader
Ron Steigerwalt, Ph.D., Pharmacology Team Leader
David Read, Regulatory Policy Management
Mary Catchings, Regulatory Policy Management

Background:

With the publishing of the FR notice dated April 20, 2000, "Parenteral Product: Drugs for Human Use: Drug Efficacy Study Implementation Amendment" which requires all approved IV Multivitamin adult formulations (11 years and older) to reformulate their drug product. After initial discussions between the Division of Metabolic and Endocrine Drug Products (HFD-510) and David Read and Mary Catchings from the Office of Regulatory Policy and Management was to have the firm commit to submitting a plan with the new formulation as outlined in the FR notice or to no approve the NDA because it did not conform to the Notice.

Meeting Objectives:

1. Discussion of whether to approve or disapprove of the NDA

2. Update on the Status of the NDAs

Decisions and Conclusions Reached:

1. The NDA can be approved with the drug product modeled after Astra's old formulation (NDA 8-809) with a commitment to submit a plan for supplementing their NDA with the new formulation as outlined in the April 20, 2000 Federal Register Notice. However,. Jane Axelrad of Office of review Management will have to sign off on this decision.

2. The following reviews or reports are still pending:

   a. Medical Review
   b. Microbiology Review
   c. Establishment Evaluation Review
   d. Labeling Review

Action Items:

	Item	Responsible Person	Due Date
1.	Reviews to be completed	Dr. Jean Temeck, Carol Vincent, Compliance	May 5, 2000
2.	Review Decision	Jane Axelrad	May 3, 2000

Minutes Preparer: /S/
may 3, 2000

Attachments/Handouts: FR Notice, April 20, 2000; FR notice September 17, 1984

cc: Original
HFD-Div. Files
HFD-/CSO/SMcCort

Drafted by:
Initialed by:
final:

MEETING MINUTES

Printed by Stephen McCort

Electronic Mail Message

ivity: COMPANY CONFIDENTIAL

Date: 02-May-2000 04:42pm
From: Lisa Rarick
RARICK
Dept: HFD-102 PKLN 13B28
Tel No: 301-827-5920 FAX 301-480-6644

O: Enid Galliers (GALLIERS)
O: John Jenkins (JENKINSJ)
O: David Orloff (ORLOFFD)

C: Stephen McCort (MCCORTS)
C: Duu Gong Wu (WUD)
ubject: Re: Action plan for Sabex Multi-12 (vitamin) Injection NDA 21-163

i Enid,

spoke with David about the Phase 4 commitment language. Please go head and use the standard-type language. Something like "We remind you f your commitment (date) to provide a plan for compliance with the pril 21, 2000 Federal Register notice (title, etc) by June 19, 2000". ou may want to also impose some timeframe for the formulation change ubmission? The chemists and/or the sponsor may have some suggested ording.

Printed by Stephen McCort

Electronic Mail Message

vity: COMPANY CONFIDENTIAL

Date: 02-May-2000 09:59am
From: David Read
READD
Dept: HFD-007 WOC2 3047
Tel No: 301-594-2041 FAX 301-827-5562

O: See Below
ubject: Sabex - Parenteral Multivitamins

r. Jenkins,

s you requested, I discussed with Jane the situation with the pending abex (b)(2) application and the recent FR notice. She agrees that we an go ahead and approve the current older formulation, and agrees that e should emphasize in the approval letter that Sabex must commit to applementing its application in acccord with the notice.

ave Read

istribution:

D: John Jenkins (JENKINSJ)

C: Jane Axelrad (AXELRADJ)
C: Mary Catchings (CATCHINGS)
C: David Orloff (ORLOFFD)
sa Rarick (RARICK)
an Temeck (TEMECK)
C: Stephen McCort (MCCORTS)

[redacted] A1721

ORIGINAL

SABEX®

Pharmaceutical Products
Produits pharmaceutiques

[redacted]

PUROLATOR

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 14 2000
HFD-510

April 11, 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 21-163 for Multi-12® (Multiple Vitamins for Infusion)**

Dear Dr. Jenkins:

The present is an amendment to our NDA 21-163 for the above-mentioned product currently under review. The information enclosed is further to an information request received from the FDA on March 31, 2000, a copy of which is herebyb enclosed. This response was forwarded by fax on today's date to the attention of Mr. Steve McCort.

We trust that the above is satisfactory. Should you require additional information do not hesitate to contact the undersigned at (450) 641-4903 Ext. 2161.

Sincerely,

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
S. mt
CSO INITIALS 5-15-00 DATE

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

Previously Received

SABEX® Pharmaceutical Products / Produits pharmaceutiques

FACSIMILE TRANSMITTAL

DATE	*2000-04-11*
ATTENTION	*Mr. Steve McCort* *Project Manager, Division of Metabolic & Endocrine Drug Products*
ADDRESSEE	*FDA, Rockville, Maryland, USA*
FACSIMILE #	*(301) 443-9282*
FROM	*Ms. Leonor Ferreira* *Tel: (450) 641-4903, ext. 2161*
NUMBER OF PAGES (INCLUDING THIS COVER PAGE): 13 *If all pages are not received, please call the SENDER at the above-mentioned number.*	

Re: Response to Information Request {NDA 21-163}

Dear Mr. McCort,

The present is a complete response, in question and answer format, to the information request we received dated March 31, 2000, a copy of which is hereby included. The present will be forwarded to FDA as an official amendement to our NDA.

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

Best regards,

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

SABEX INC
145 Jules-Leger Street
Boucherville, QC, Canada
J4B 7K8
Tel : 514-641-4903
Fax : 514-596-0003

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 10, 2000
Time: 11:30 am
Location: PKLN 14B-56

Application: NDA 21-163

Drug: Multi-12 (Multiple Vitamins for Infusion)

Type of Meeting: Labeling Meeting

Meeting Chair: David Orloff, M.D.
Medical Team Leader

Meeting Recorder: Steve McCort
Project Manager

Attendees:

David Orloff, M.D., Medical Team Leader
Jean Temeck, M.D., Medical Reviewer
Duu-Gong Wu, Ph.D., Chemistry Team Leader
David Lewis, Ph.D., Chemistry Reviewer
Hae Young Ahn, Ph.D., Biopharm. Team Leader
Robert Shore, Pharm D., Biopharm Reviewer
Ron Steigerwalt, Ph.D.,Pharmacology Team Leader

Background: The Firm submitted labeling for this drug product dated July 19, 1999. The labeling for this product was modeled after Astra's MVI-12 product, NDA 8-809.

Decisions: The July 19, 1999 draft labeling was reviewed by the review team. The recommendations are as follows:

Chemistry: No Changes in Labeling

Pharmacology: Addition of labeling for sections **Carcinogenicity, Mutagenicity,** and **Impairment of Fertility and Pregnancy Category C.**

Medical: Recommended changes will communicated to the Project Manager at a later date.

Biopharm: Minor changes in typos in the labeling.

Action Item:

All revisions to the July 19, 1999 labeling will be communicated to Project Manager before communicating with the Firm.

/S/

Steve McCort, Project Manager, HFD-510

cc: NDA 21-163
HFD-/Div. Files
HFD-/CSO/SMcCort

MEETING MINUTES

FOOD AND DRUG ADMINISTRATION
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: **March 31, 2000**

TO:		FROM:	
Name:	**Leonor Ferreira**	Name:	**Steve McCort**
Fax No:	514-596-1460	Fax No:	301-443-9282
Phone No:	450-641-4903	Phone No:	301-827-6415
Location:	SABEX	Location:	FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

Comments:

INFORMATION REQUEST (CHEM) FOR PENDING NDA 21-163 MULTI-12

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

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

DATE RECEIVED: March 8, 2000	DUE DATE: April 12, 2000	OPDRA CONSULT #: 00-0078

TO: John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Steve McCort, Project Manager
HFD-510

PRODUCT NAME: Multi-12 (multiple vitamins for infusion) NDA #: 21-163	MANUFACTURER: Sabex, Incorporated Boucherville, Qc, Canada J4B 7K8

SAFETY EVALUATOR: Carol Pamer, R.Ph.

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

OPDRA RECOMMENDATION: From a safety perspective, OPDRA has no objections to the use of the proprietary name "Multi-12". However, we recommend that the term —— be associated with the tradename, e.g. "Multi-12™ —— " (see attached review). The established name of this product needs to be revised to comply with the USP/NF standards. We have also made recommendations for labeling revisions to minimize potential errors with the use of this product. See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

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

/S/
Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 5, 2000

NDA NUMBER: 21-163

NAME OF DRUG: Multi-12 (multiple vitamins for infusion)

NDA HOLDER: Sabex, Incorporated
Boucherville, Qc, Canada J4B 7K8

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the tradename "Multi-12". Multi-12 is a parenteral multiple vitamin preparation that must be diluted prior to infusion. The product is indicated as a daily multivitamin maintenance supplement for adults and children aged 11 and older who are receiving parenteral nutrition. Multi-12 is also indicated for other conditions in which administration of a vitamin by the intravenous route is required (e.g., surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states). It is supplied as a kit containing two 5-ml vials that collectively contain 12 vitamins.

The vitamin content of Multi-12 is identical to that of an existing U.S. product, M.V.I.-12™ (MVI-12) (AstraZeneca). The sponsor previously submitted an ANDA to the Office of Generic Drugs. This application was not approved, due to a concern that the concentration of the inactive ingredient polysorbate-80 differs from that of MVI-12. Polysorbate-80 is used to solubilize the fat-soluble vitamins in an aqueous solution and has been suspected of toxicities in the pediatric population. However, the sponsor has been granted a bioequivalence waiver by HFD-510 and, therefore, this product will be considered bioequivalent to MVI-12. (Source: personal communication, HFD-510)

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[ii] American Drug index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[iii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

look alike to Multi-12 to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted two (2) prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

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

The reference product *M.V.I.-12* was considered to have significant potential for confusion with Multi-12.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 62 health care professionals (nurses, pharmacists, physicians) to determine the degree of confusion of Multi-12 with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient medication order, along with a combination of marketed and unapproved drug products and an order for Multi-12 (see below). This written prescription was optically scanned and delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient order 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 email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Inpatient: D5½NS w/Multi 12 at 80mL/hr	*Inpatient*: D5½ normal saline with Multi 12 at 80cc per hour.

2. Results

Results of this exercise are summarized below:

Study	No. of participants	# of responses (%)	"Multi-12" response	Other response
Verbal: Inpatient	31	18 (58%)	14 (78%)	4 (22%)
Written: Inpatient	31	18 (58%)	6 (33%)	12 (66%)
Total:	62	36 (58%)	20 (56%)	16 (44%)

[iv] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-99, and the electronic online version of the FDA Orange Book.
[v] WWW location http://www.uspto.gov/tmdb/index.html.

Among participants in the written prescription study, 6 (33%) of the respondents provided the correct spelling of the name Multi-12. Seven (7) participants interpreted the name as multivitamin-12 or multivitamins-12, one with a quantity of 10 mL specified, the usual dose of MVI-12. *One respondent interpreted the name as MVI-12*. The other name interpretations were generally close variations of the drug name.

Among verbal prescription study participants, the majority (14 of 18, 78%) of the study participants interpreted the name correctly. *Two (2) respondents interpreted the name as MVI-12.* The other interpretations were phonetic variations of Multi-12.

C. SAFETY EVALUATOR RISK ASSESSMENT

There was one significant sound-alike, look-alike name identified in the Expert Panel review of the proprietary name "Multi-12", the reference product "M.V.I.-12".

We conducted prescription studies in an attempt to simulate the prescription ordering process. In this exercise, 3 study participants either interpreted the drug name as MVI-12. However, the active ingredients of these two products are identical and Multi-12 will be considered bioequivalent to MVI-12. A facility would also be likely to stock only one brand of this preparation as well, with the product selection being made at the supply reordering stage.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

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

A. PACKAGING

1. Although it is necessary for reasons of chemical incompatibility among the vitamin components to have two separate vials to complete the 12-vitamin supplementation, based on previous experience with evaluation of medication errors, this type of packaging configuration is error-prone. *We suggest, therefore, that the sponsor add the word ~~____~~ to the product name, e.g.~~_____~~* This will provide an additional reminder to personnel using the product that each component individually does not comprise a complete dose.

2. *We would recommend that the product only be packaged in single cartons with 2 vials.* The firm's proposal to have a carton of 5's (5 vials of Vial 1 and 5 vials of Vial 2) unnecessarily increases the risk of personnel compounding a solution with 2 identical vials, resulting in the wrong dose being administered.

B. CONTAINER LABEL (single- and five-dose packages)

1. The established drug name chosen by the manufacturer for this product, "multiple vitamins for infusion" is a pharmaceutical dosage form that is not officially recognized by the United States Pharmacopeia in their official compendia. Including the phrase "for infusion" in the established drug name is also a safety concern in that the user may assume that the undiluted product is ready for infusion, the reverse of the likely intent of the manufacturer.

We suggest that the established name be revised, based upon the USP/NF[vi]*, to :* _____ _____; *with appropriate labeling specifying that the product must be diluted.* Sponsors who market related products should also revise the name of this product accordingly.

2. In the designation of multivitamin content, *we recommend substitution of "mcg" or "micrograms" for the symbol "μg"*, as the Greek symbol is often mistaken for "mg", resulting in a 10-fold overdose.

3. We recommend revision of the statement *"For intravenous infusion only" to "Must be diluted".*

4. *Revise the statement "Caution: Rx only. Federal law prohibits dispensing without prescription" to "Rx only"*, per the FDA Modernization Act of 1997.

5. Revise the statement "Each 5mL of Vial 1 [or 2] *provides:*" to "Each 5mL...*contains:*".

6. Delete statement "Consult package insert for dosage and full prescribing information" and *replace with "Usual dosage: See package insert."*

C. CARTON LABELING and PACKAGE INSERT LABELING

1. For clarity, on front panel, *revise the section entitled "Contents"* to "Contains 5 each of Vial 1 and Vial 2" or a related statement. The use of "5 x" does not convey a clear meaning. Similar use of the abbreviation appears under "How Supplied" in the package insert and should be revised.

2. Under Dosage and Administration, for consistency with the carton label, *revise statement "Store between 2-8 [degrees] C (36-46 [degrees] F)"* to "Store under refrigeration between 2-8 [degrees] C (36-46 [degrees] F)".

3. See also comments as stated above.

[vi] USP 24/NF 19: U.S. Pharmacopeia and National Formulary, 1999, The United States Pharmacopeial Convention, Inc., Rockville, MD, p.2112, "Injections" and p. 2312, "Nutritional supplements".

IV. RECOMMENDATIONS

1. From a safety perspective, OPDRA has no objections to use of the proprietary name "Multi-12". However, we recommend that the term [redacted] be associated with the tradename, e.g. "[redacted]" (see "PACKAGING" above). OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated.

2. We have made recommendations for labeling revisions to minimize potential errors with the use of this product.

3. The established name of this product needs to be revised to comply with USP/NF standards. The Labeling and Nomenclature Committee (LNC) should be consulted regarding this issue.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

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

Concur:

/S/

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

cc: NDA 21-163
HFD-510; Division Files/Steve McCort, Project Manager
HFD-510; John Jenkins, Acting Division Director
HFD-040; Mark Askine, Senior Regulatory Review Officer, DDMAC
HFD-440; Lanh Green, Safety Evaluator, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Peter Honig, Director, OPDRA (electronic copy)
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (electronic copy)

L:\OPDRA00\PAMER\000022MULTI12.fin.DOC

SABEX®

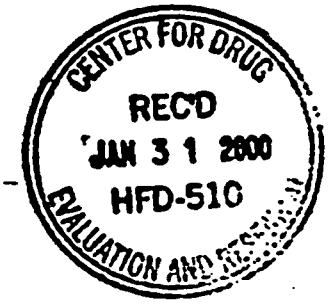
Pharmaceutical Products
Produits pharmaceutiques

PUROLATOR

ORIG AMENDMENT
BC

ORIGINAL

January 28, 2000



Solomon Sobel, 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 21-163 for Multi-12® (Multiple Vitamins for Infusion)**

Dear Dr. Sobel:

The present is an amendment to our NDA 21-163 for the above-mentioned product currently under review. The information enclosed, obtained from Lonza and pertaining to their drug substance Niacinamide, was submitted originally by e-mail to Dr. David Lewis.

We trust that the above is satisfactory. Should you require additional information do not hesitate to contact the undersigned at (450) 641-4903 Ext. 2161.

Sincerely,

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

REVIEWS COMPLETED
DATE

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

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

SABEX®
Pharmaceutical Products
Produits pharmaceutiques

January 12, 2000

PUROLATOR

Solomon Sobel, 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 21-163 for Multi-12® (Multiple Vitamins for Infusion)

Dear Dr. Sobel:

The present is an amendment to our NDA 21-163 for the above-mentioned product currently under review. Enclosed are the originals of the fax sent January 12, 2000 to Dr. David Lewis.

We trust that the above is satisfactory. Should you require additional information, please do not hesitate to contact the undersigned at (450) 641-4903, extension 2161.

Sincerely,

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

LF/lfa

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

Encl.

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

ORIGINAL

SABEX®

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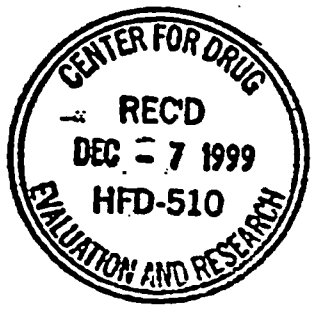
Produits pharmaceutiques

Bc.

FEDERAL EXPRESS

December 6, 1999



Solomon Sobel, 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 21-163 for Multi-12® (Multiple Vitamins for Infusion)**

Dear Dr. Sobel:

The present is an amendment to our NDA 21-163 for the above-mentioned product currently under review. The information enclosed was submitted by fax to Dr. David Lewis. Enclosed are the originals of the faxes in question, one dated November 18, 1999, and the second November 29, 1999.

We trust that the above is satisfactory. Should you require additional information do not hesitate to contact the undersigned at (450) 641-4903 Ext. 2161.

Sincerely,

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

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

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

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 10, 1999
Time: 11:30 am
Location: PKLN 14B-56

Application: NDA 21-163

Drug: Multi-12 (Multiple Vitamins for Infusion)

Type of Meeting: 45 day Filing Meeting

Meeting Chair: David Orloff, M.D.
Medical Team Leader

Meeting Recorder: Steve McCort
Project Manager

Attendees:

David Orloff, M.D., Medical Team Leader
Jean Temeck, M.D., Medical Reviewer
Duu-Gong Wu, Ph.D., Chemistry Team Leader
David Lewis, Ph.D., Chemistry Reviewer
Hae Young Ahn, Ph.D., Biopharm. Team Leader
Robert Shore, Pharm D., Biopharm Reviewer
Ron Steigerwalt, Ph.D.,,Pharmacology Team Leader

Decisions:

1. All disciplines agreed that the NDA is fileable.

2. The following planning dates were agreed upon:

   Date reviews to be completed - April 21, 2000
   Date to Division Director - May 5, 2000
   Date letter to be signed - May 19, 2000

Minutes Preparer: /S/

9-13-00

cc: NDA 21-163
HFD-/Div. Files
HFD-/CSO/SMcCort

Drafted by:
Initialed by:
final:

MEETING MINUTES

NDA 21-163

JUL 26 1999

SABEX INC.
Attention: Susanne Levesque
Vice President, Quality Assurance & Regulatory Affairs
145 Jules-Leger Street
Boucherville, QC, Canada J4B 7K8

Dear Ms. Levesque:

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® (Multiple Vitamins for Infusion)

Therapeutic Classification: Standard (S)

Date of Application: July 19, 1999

Date of Receipt: July 20, 1999

Our Reference Number: NDA 21-163

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 September 18, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 20, 2000, and the secondary user fee goal date will be July 20, 2000.

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/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
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-163
HFD-510/Div. Files
HFD-510/S.McCort
HFD-510/JTemeck/DOrloff/HAhn/MFossler/DWu/DLewis/RSteigerwalt
HFD-510/SSobel
HFD-510/EGalliers
DISTRICT OFFICE

Drafted by: smm /July 26, 1999
final: smm/July 26, 1999
filename: N21163.ACK

ACKNOWLEDGMENT (AC)

SABEX®

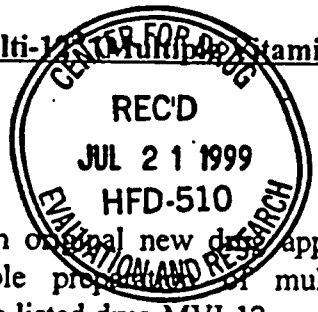
Pharmaceutical Products
Produits pharmaceutiques

July 19, 1999

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 (Multiple Vitamins for Infusion)**



Dear Sir or Madam:

SABEX INC. hereby submits an original new drug application ("NDA") seeking approval to market **Multi-12®**, an injectable preparation of multiple vitamins for infusion that is pharmaceutically equivalent to the listed drug MVI-12, manufactured by Astra, pursuant to NDA# N008809. This submission is being submitted as a 505(b)(2) application.

This NDA consists of 16 volumes. SABEX is filing an archival copy (in blue folders) of the NDA will 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 as well as 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 tittle or abbreviation thereof, for that subsection.

.../2

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

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

A field copy (burgundy folders) containing a true complete copy of the CMC and Microbiology technical sections of this NDA is also included.

Please note that the labelling of this product is consistent with the labelling of the listed and US reference product MVI-12. Furthermore, please be informed that this product is intended solely for adults and children 11 and older. A pediatric version of this formulation exists on the market which differs from the adult formulation.

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
SABEX INC.
145 Jules-Leger Street
Boucherville, (QC), CANADA J4B 7K8

Phone: (450) 641-4903 ext. 2161
FAX: (514) 596-1460

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

We trust that the enclosed application is satisfactory.

Sincerely,

SABEX INC.
Suzanne Levesque, B.Pharm., MBA
Vice President, Quality Assurance & Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-163

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
SABEX INC.	June 28, 1999
TELEPHONE NO. *(Include Area Code)* (450) 641-4903	**FACSIMILE (FAX) Number** *(Include Area Code)* (514) 596-1460
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 145, Jules-Leger Street Boucherville, Quebec CANADA J4B 7K8	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Ken Muhvich, Ph.D. 1818 Circle Road Ruxton, Maryland USA 21204 Phone: (410) 823-6317 Fax: (410) 823-6318

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Multiple Vitamins for Infusion	MULTI-12

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)* CDR

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
INJECTABLE	See attachment A at end of form 356h	IV Infusion

(PROPOSED) INDICATION(S) FOR USE: Daily multi vitamin maintenance supplement for adults and children aged 11 and older receiving parenteral nutrition.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 20 1999
CDR

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application	
M.V.I.-12	ASTRA	N008809 004

TYPE OF SUBMISSION (check one)
☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION: MARKETING APPROVAL

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 16 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See ATTACHMENT B at end of form 356h
To the best of our knowledge these sites are ready for inspection.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

	This application contains the following items: *(Check all that apply)*
X	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
X	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Suzanne Levesque	Suzanne Levesque, B.Pharm.,MBA Vice President, RA/QA	July 13, 1999

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
145, Jules-Leger Street, Boucherville, Qc CANADA J4B 7K8	(450) 641-4903, ext. 2142

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

01 008

1. APPLICANT'S NAME AND ADDRESS

SABEX INC.
145, Jules-Léger Street
Boucherville, Québec
Canada J4B 7K8

2. TELEPHONE NUMBER *(Include Area Code)*

(450) 641-4903

3. PRODUCT NAME

MULTI-12

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. NO 505 (B) (2) APPLICATION

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

N/A

6. LICENSE NUMBER / NDA NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

APPLICATION EXEMPT ☐ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

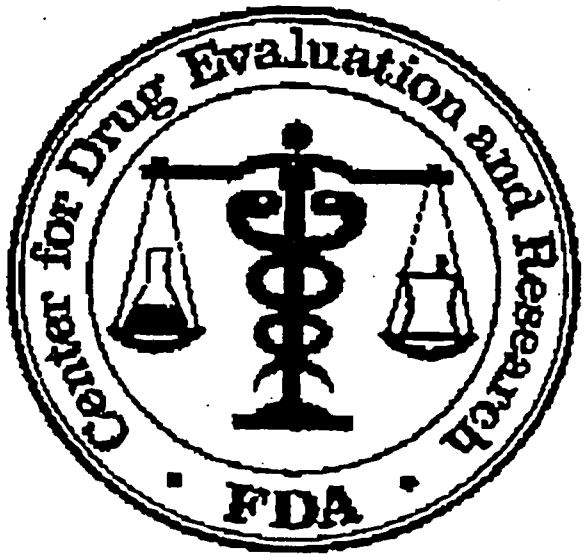
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Vice-President Scientific Affairs	June 25/1999

FORM FDA 3397 (5/98)

01 016

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: APRIL 7, 1999



TO:		FROM:	
Name:	LEONOR FERREIRA	Name:	Steve McCort
Fax No:	514-596-1460	Fax No:	301-443-9282
Phone No:	450-641-4903	Phone No:	301-827-6415
Location:	SABEX PHARM	Location:	FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

Comments:

CONFIRMATION OF MEETING WITH FDA

SABEX®

Pharmaceutical Products
Produits pharmaceutiques

PERSONAL and CONFIDENTIAL

FEDERAL EXPRESS

September 24, 1998

Mr. Steve McCort
Project Manager, Division of Metabolic & Endocrine Drug Products
FDA
Document Control Room 14B-19
5600 Fisher's Lane
Rockville, Maryland, USA 20857

Re: Multi-12® (Multiple Vitamins for Infusion)

Dear Mr. McCort:

Please find enclosed a copy of our notes from the Pre-NDA meeting held on September 15, 1998. The question numbering is as per the package but I have also included the corresponding slide presentation question number.

Should you have any questions or comments do not hesitate to contact me.

Sincerely,

SABEX INC.
Leonor Ferreira, M.Sc., MBA
International Regulatory Affairs Specialist

LF/
att.

SABEX INC
145 Jules-Leger
Boucherville, QC, Canada
Tel : 514-641-4903
Fax : 514-596-0003

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