DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date . NOV 1

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

Subject 75-day Premarket Notification for New Dietary Ingredient

TO Dockets Management Branch, HFA-305

New Dietary Ingredients:	Respivax
Firm:	Biocare medical Technology, LLC on behalf of N/A/T/O International
Date Received by FDA:	October 4, 1999
90-day Date:	January 1, 2000

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-03 16 after January 1, 2000.

Robert J. Moore, Ph.D.

95S-0316

RPT56

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

NOV 15 1999

Mr. David Balzer
Biocare Medical Technology, LLC
660 Main Street South
Suite 7
Woodbury, Connecticut 06798

Dear Mr. Balzer:

This letter is in response to your submission pursuant to 21 U.S.C. 350b(a)(2) to the Food and Drug Administration (FDA) on behalf of N/A/T/O International, received on October 4, 1999, for a substance that you assert is a new dietary ingredient. Your submission notified FDA of the intent of your client to market a product named "Respivax" that contains killed, freeze-dried lysates and bacterial bodies of *Streptococcus pneumoniae. Neisseria catarrhalis, Streptococcus pyogenes*, *Haemophilus influenzae*, *Staphylococcus aureus,* and *Klebsiella pneumoniae.*

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe, FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 2 1 U.S.C. 342(f)(l)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the product you intend to market. Those concerns are set forth below.

The product is not a dietary supplement as defined in 21 U.S.C. 321(ff).

Respivax is not a dietary supplement because it does not meet the statutory definition of a dietary supplement in that freeze dried lysates and bacterial bodies are not "dietary ingredients" as defined in 21 U.S.C. 321(ff)(1). These ingredients are not vitamins, minerals, herbs or other botanicals, amino acids, or concentrates, metabolites, constituents, extracts or combinations of any ingredient described above. These ingredients in your product also are not "dietary substances" that increase the "total dietary intake" because they cannot reasonably be viewed as part of man's usual food or drink. The substances in your product are composed of pathogenic microorganisms. Pathogens are not substances that are food or that are used for food. Therefore, your product is not a dietary supplement.

The submission does not establish that a product containing the subject "new dietary ingredient" is reasonably expected to be safe.

Even if Respivax could meet the definition of a dietary supplement, it would violate other provisions of the Federal Food, Drug, and Cosmetic Act (the Act). The evidence on which you rely does not support your conclusion that a dietary supplement containing the ingredients named above, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe.

Your submission contained summary results of animal studies that you assert are adequate to evaluate the safety of ingested Respivax. The data from the animal studies you submitted are not adequate to evaluate the long-term safety of this product when used in humans. The information submitted is inadequate to determine if the studies are appropriately designed to provide the type of data necessary to evaluate the safety of a dietary ingredient intended to be consumed by humans. The data result in significant uncertainty in making dose comparisons and assessing the safety or hazards associated with human consumption of a dietary supplement containing this ingredient.

You also assert that the use of this product outside the United States evidences that it "is completely safe and non-toxic" and that there have been no "reports of side effects or illness attributable to the Respivax." However, you provide no evidence to support these assertions and, therefore, its use elsewhere is not a basis for concluding that the dietary supplement containing the new dietary ingredient is reasonably expected to be safe.

Furthermore, the product is not adequately characterized to enable a careful examination of the potential hazards such a product might pose. There is no information in the submission regarding the potential presence of bacterial toxins in this product. More importantly, the specific strains of the microorganisms in the product are not identified. Consequently, it isn't possible to identify and critically evaluate risks that may be associated with the use of a lysate containing a particular organism. For example, Group A *Streptococcus* contain antigenic substances known to cross react with cardiac tissue and that may play a role in heart disease. The use of type a *H. influenzae* would raise different safety concerns than would the use of type b *H. influenzae*. Moreover, the information in the submission is not only inadequate for a determination of what risks may be associated with the use of this product as a dietary supplement, it indicates that the firm has not even considered such issues.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that Respivax, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, even if your product were a dietary supplement (which as discussed above, it is not), it would be adulterated under 21 U.S.C. 342(f)(l)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 2 1 U.S.C. 33 1 (a) and (v).

Respivax appears to be a biological product as defined in 42 U.S.C. 262 [section 351 of the Public Health Service Act]

"[T]he term 'biological product' means a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease" 42 U.S.C. 262 (see 21 CFR 600.3(h)). FDA has information that this product is licensed with the National Drug Institute (Bulgaria) and that in Bulgaria it is used for the prevention and treatment of chronic and acute respiratory diseases in children and adults. The agency has also been provided published scientific studies that describe this product's use to treat or prevent diseases caused by pathogenic microorganisms. Based on the nature of the ingredients in your product, the effect of those ingredients on the body, and publically available information about the use of this product, it appears to be a biological product as defined in 42 U.S.C. 262. A biological product-inust be licensed prior to being marketed in the United States. 42 U.S.C. 262.

Respivax also appears to be a drug under 21 U.S.C. 321(g)(l)(B).

FDA has statements, made by foreign government officials responsible, in part, for the manufacture of Respivax, that state that the product is produced and used for the prophylaxis and treatment of chronic and acute respiratory diseases in children and adults. These statements also declare that the product is licensed with the National Drug Institute (Bulgaria). Based on this information, this product appears to be intended for use in the treatment, cure, prevention, mitigation, or diagnosis of disease. Therefore, the product appears to be a drug under 21 U.S.C. 321(g)(l)(B) and would be subject to regulation under the drug provisions of the Act.

In sum, your product is not a dietary supplement. Rather, it appears to be a biological product and drug that must be licensed, or otherwise preapproved, before being marketed in the United States.

Please contact us if you have any questions concerning this matter.

Sincerely,

Lynn A. Larsen, Ph.D.
Director
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety
and Applied Nutrition

Biocare Medical Technology, LLC
660 Main Street South, Suite 7
Woodbury, CT 06798

Tel: (203) 263-5951
Fax: (203) 263-5956

6-7484

28 September, 1999

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C. Street SW
Washington, DC 20204

RECEIVED
10/4/99

-Cover Letter-

[Original Copy]

PREMARKET NOTIFICATION: Dietary Supplement- Respivax

Dear Sirs:

In accordance with the requirements listed in the Code of Federal Regulations, [21 CFR Section190.6], I am hereby submitting a premarket notification for the dietary supplement known as Respivax.

As the official correspondent for the N/A/T/O International, the distributor of Respivax, I respectfully request that all correspondence regarding this filing by directed to Biocare Medical Technology, LLC. My address, phone and fax numbers are listed above.

Please do not hesitate to contact me should you have any questions concerning this premarket notification.

Sincerely,

David Balzer
Official Correspondent for
N/A/T/O International

Distributor:

The complete name and address of the distributor for Respivax is:

N/A/T/O International
Corporate Office
#9- 18 18 Cornwall Avenue
Vancouver, British Columbia
Canada V6J lC7

Dietary Ingredient:

Respivax contains a mixture of microbial lysates and heat-killed microbes that have been lyophilized. Although widely distributed in Europe and the Far East over the past ten (10) years, there appears to be no evidence that these ingredients were available for sale in the U.S. prior to October 15, 1994.

The freeze-dried mixture includes: Streptococcus pneumonia, Neisseria catarrhalis, Streptococcus pyogenes, Hemophilus influenzae, Staphylococcus aureus and Klebsiella pneumoniae.

Description:

Level of Dietary Ingredients:

Respivax will be offered in three different tablet forms. Each form varies in the amount of the dietary ingredient it contains. The three levels of dietary ingredients found in the tablets are: 50 mg (1.25×10^9 microbial bodies of each strain), 25 mg (0.625×10^9 microbial bodies of each strain) and 10 mg (0.250×10^9 microbial bodies of each strain).

Recommended Use:

ADULTS: One (1) 50 mg tablet before breakfast every day for 120 days. Thereafter, one (1) 10 mg tablet every day before breakfast.

CHILDREN [ages 3 to 14]: One (1) 25 mg tablet before breakfast every day for 120 days. Thereafter, one (1) 10 mg tablet everyday before breakfast.

History of Use and Safety:

Respivax is completely safe and non-toxic. It has been sold throughout Europe and the Far East for more than ten (10) years. During that time, thousands of bottles have been distributed and consumed. The product has been utilized by children over the age of 3 as well as adults. At no time have there been any reports of side effects or illness attributable to the Respivax. The product may be used safely in combination with any treatment or food. It is also safe for use during pregnancy and lactation.

Microbial Activity:

The distributor of Respivax contracted the Canadian Analytical Laboratories, Inc. to perform a microbial analysis of the product per USP 23<2021>. The results demonstrate the product's lack of microbial activity and acceptability for human consumption.

Copy of laboratory results in attached as Exhibit A.

Toxicity:

The National Center of Infectious and Parasitic Diseases of Sofia, Bulgaria controls the manufacturing of Respivax. Their Deputy Director, under the auspices of the Bulgarian Ministry of Health, conducted both acute and chronic toxicity tests of Respivax.

The results demonstrate the product's suitability for human consumption.

Copy of the toxicity test results is attached as Exhibit B.

Signature of Responsible Party:

As the Official Correspondent for the distributor, I am hereby asserting that the information contained in this premarket notification is, to the best of my knowledge, truthful and accurate.

Signed:

David R. Balzer, Jr.
Official Correspondent
N/A/T/O International

EXHIBIT A

Canadian analytical laboratories inc.

1275 Morningside Avenue, Unit 13, Scarborough, Ont. M1B 3W1 • Tel: 286-3332 • Fax: 286- 3885

** CERTIFICATE OF ANALYSIS **

CUSTOMER	PRODUCT		
NATO INTERNATIONAL 1380 BURRARD STREET VANCOUVER, B.C. V6Z 2H3	RESPIVAX	AR NO.: DATE: CUST PO NO.: LOT NO: DIN NO: FILE NO:	9917447 APR-14-1999 030296 RESPIVAX
		PAGE:	1

ATTN: MR. ROBERT EDWARDS

TESTS	METHOD	SPECIFICATIONS	RESULTS
TOTAL PLATE COUNT	USP 23 <2021>	N.M.T. 10,000 COL/G	L.T. 10 COL/G
E. coli	USP 23 <2021>	NEGATIVE	NEGATIVE
SALMONELLA	USP 23 <2021>	NEGATIVE	NEGATIVE
YEAST	USP 23 <2021>	N.M.T. 1,000 COL/G	L.T. 10 COL/G
MOLD	USP 23 <2021>	N.M.T. 1,000 COL/G	L.T. 10 COL/G
STAPHYLOCOCCUS AUREUS	USP 23 <2021>	NEGATIVE	NEGATIVE
PSEUDOMONAS AERUGINOSA	USP 23 <2021>	NEGATIVE	NEGATIVE

MR. CHARLES NG, DIRECTOR OF LABORATORIES — DATE April 19th/99

BOOK REF:
ANALYST: J.K.
CHECKED BY:

APPROVED BY:
DR. CHRISTIAN SOOD, DIRECTOR OF OPERATIONS — DATE April 19th/99

THE TRANSLATORS AND INTERPRETERS Ltd

София 1000, ул. Граф Игнатиев 16; 1000 Sofia, 16 Graf Ignatiev Str., P.O.B. 161
(+359 2) 980-28-72; 980-08-98; 86-08-38; 67-46-15; 981-74-00

Translation from Bulgarian

NATIONAL CENTRE OF INFECTIOUS AND PARASITIC DISEASES
SOFIA

STUDY OF THE TOXICITY OF "RESPIVAX" PREPARATION

ACUTE TOXICITY

A/ Acute toxicity of white mice

30 mice of the ICR strain and weight of 18–20 gr were used for this purpose. Twenty of them were fed per os by a probe for a period of 5 days the daily dose being 50 mg of Respivax in a volume of 0.6 ml physiological solution. This Respivax dose is equivalent to about 5000 human doses. All mice were under daily control with regard to their general condition, nutrition and weight and blood was taken from them for establishing their basic hematologic parameters (erythrocytes, leucocytes, hemoglobin and differential count).

On the second day after the last feeding, the aminals were dissected under a weak ether narcosis for macroscopic observation. Material was taken from the main parenchymal organs (lungs, liver, spleen and brain) for a histological and electronic–microscopic study.

Am a result of the stud&s no changes were established in the general condition of the animals under Respivax treatment (with regard to weight and behaviour), compared to the control group. The hematological parameters were within the norm for both groups. The histological and electronic–microscopic study did not establish any pathological changes in the studied organs.

B/ Acute toxicity of rabbits

15 "Chinchilla" rabbits of 1,500–1,600 gr weight were used for this purpose. Ten of them were fed by a probe for a period of 5 days the daily dose being 2 gr of Respivax in a volume of 2 ml physiological solution, which is a dose equivalent to about 2000 human doses. Five rabbits received 2 ml of physiological solution under the same scheme, All rabbits were under daily control with regard to their general condition, nutrition and weight, and blood

was taken from them for establishing their basic hematologic parameters (erythrocytes, leucocytes, hemoglobin and differential count).

On the second day after the last feeding, the aminals were dissected after being treated intravenously with 300 mg Hexobarbital Natrium, manufactured by Veb Arzvelmittelwern, Dresden. Macroscopic observation was performed and material was taken from the main parenchymal organs (lungs, liver, spleen and brain) for a histological end electronic–microscopic study.

As a result of the studies no change8 were established In the general condition of the animals under Respivax treatment (with regard to weight *and* behaviour), compared to the control group. The hematological parameters were within the norm for both groups. The histological and electronic–microscopic study did not establish any pathological changes in the studied organs.

CHRONIC TOXICITY

Chronic toxicity of rats

30 rats of the Wistar breed and weight of 180–200 gr were used for this purpose. Twenty of them were fed per os by a probe for a period of 4 months the daily dose being 0.5 gr of Respivax in a volume of 1 ml physiological solution. The rats were under daily control with regard to their general condition (weight, nutrition, sick and death rate). The hematologic parameters of both groups were studied every month during the 4–month period. Seven days after the end of the test, the aminals were dissected under a weak ether narcosis for macroscopic observation. Material was taken from the main parenchymal organs (lungs, liver, spleen and brain) for e histological and electronic–microscopic study.

As a result of the studies no changes were established in the general condition of the animals under Respivax treatment (with regard to weight and behaviour), compared to the control group. The hematological parameters were within the norm for both groups. The histological and electronic–microscopic study did not establish any pathological changes in the studied organs.

Deputy Director of Manufacture: (sgd.ill.)
Prof.Pl.Nenkov, D.Sc.
SEAL of the National Centre of Infectious and Parasitic Diseases.

Certified by the Ministry of Health under No 4314/05.07.1999.

Sworn translator:
T.Kostova

AUG-25-1999 17:09 NATO INTERNATIONAL
BULGARIAN TRANSLATIONS 604 734 5131 P.06/06

Преводачите ООД

THE TRANSLATORS AND INTERPRETERS Ltd

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Translation From Bulgarian

NATIONAL CENTER Of INFECTIOUS AND PARASITIC DISEASES
SOFIA

CERTIFICATE

RESPIVAX is produced according to a technology, which includes steps ensuring the total lack of live cells From the bacterial strains used In the production.

The quality control during the production and the analysis of the final product assure its safety.

Head of Quality Control Laboratory:

(sgd.ill.)
Prof.Dr. Roumen Manahilov

SEAL of the National Centre of Infectious and Parasitic Diseases

Sworn translator:
T.Kostova