CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-900

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-900

Alimenterics Inc.
Attention: Janet George Murnick, Ph.D.
301 American Rd.
Morris Plains, NJ 07950

AUG 16 1997

Dear Dr. Murnick:

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: ^{13}C-Urea

Therapeutic Classification: Standard

Date of Application: August 8, 1997

Date of Receipt: August 11, 1997

Our Reference Number: 20-900

We have not received the appropriate user fee for this application. Under section 736(e) of the Prescription Drug User Fee Act of 1992 (PDUFA), an application is considered incomplete and will not be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

If checks are to be sent by a courier that requires a street address, they can be forwarded to the following address:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: **This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) is on the enclosed check.**

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment was received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-900

Alimenterics, Inc.
Attention: Janet George Murnick, Ph.D.
301 American Rd.
Morris Plains, NJ 07950

AUG 26 1997

Dear Dr. Murnick:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for ^{13}C-Urea.

You were notified in our letter dated August 16,1997 that your application for ^{13}C-Urea was not accepted for filing due to non-payment of fees required under the Prescription Drug User Fee Act of 1992.

This is to notify you that the Agency has received all fees owed and your application has been accepted as of August 26, 1997.

Unless we notify you within 60 days of the above 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 October 24, 1997 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

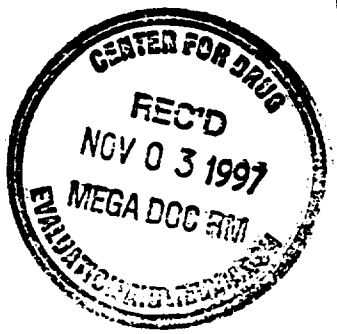
Sincerely yours,

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Alimenterics

NEW CORRESP
NC



October 27, 1997

Robin Anderson, RN, MBA
Project Manager
Division of Special Pathogens and
Immunologic Drug Products (HFD-590)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-900

Dear Ms. Anderson:

This is in response to the unofficial correspondence we received from you dated October 22, 1997 requesting specific designation of and justification for Alimenterics, Inc.'s claimed categorical exclusion from the requirement for preparation of an environmental assessment in connection with the above-referenced New Drug Application ("NDA").

The active moiety covered by Alimenterics' NDA is ^{13}C Urea, 99% enriched. Approval of Alimenterics' NDA is expected to increase the use of this active moiety as Alimenterics has not previously held an approved NDA for its use. The increased use, however, is expected to aggregate less than [redacted] annually, i.e., Alimenterics expects to distribute less than that amount of finished drug product on an annual basis. The active moiety is metabolized upon ingestion by patients. Thus, the estimated concentration of the active moiety at the point of entry into the aquatic environment, if at all, will be substantially [redacted]

It also should be noted that the ^{13}C used in the synthesis of the active moiety is a stable, nonradioactive, naturally-occurring isotope of carbon. Use of this isotope in synthesis of the active moiety and in the finished dosage form, at the levels described above, will have no significant effect on the concentration or distribution of the isotope in the environment.

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 973 285 3100 Fax 973 285 1872

Thus, pursuant to 21 C.F.R. § 25.31, Alimenterics claims categorical exclusion from the preparation of an environmental assessment in connection with NDA 20-900. Please do not hesitate to call me if you have any further questions or comments on this matter.

Sincerely,

/S/

Janet George Murnick, Ph.D.
President

cc: Edward M. Basile
R. Anthony Howard, Jr.

APPEARS THIS WAY
ON ORIGINAL

Appendix #2

Alimenterics

November 10,1997

Dr. Robert Hopkins, Medical Officer
Div. Special Pathogen and
Immunologic Drugs Products, HFD - 590
Food & Drug Administration
Rockville, MD 20852

Subject: [redacted] Pivotal Study and Cold Trap Study Reformatted Data Tables

Dear Dr. Hopkins:

Dr. Dubois from CDRH passed along a request from you to submit an analysis based on reformatting some of our data. It involved data we submitted as part of premarket notification application [redacted]

The data for submission were broken down into four groups:

1. Enrolled population - include all patients enrolled in the study, including those that were not exposed to the urea breath test (UBT).

2. Safety population - all subjects that were administered the UBT.

3. Intent to Treat (ITT) population - those subjects that had results for at least 2 reference tests as well as the UBT.

4. Efficacy population - this includes only those subjects with all test results and no protocol violations.

The enclosed tables, sent to you by fax, were prepared using the enrolled population and do not reflect those patients that were withdrawn from the study. I will send the original of this letter to the CDRH Document Control Center so it I will be added to the file and so Dr. Dubois will receive a copy.

Please let me know if you need any additional information to facilitate your review of our application.

Respectively,

Larry Christman

C. Lawrence Christman, PhD
Director Regulatory Affairs
and Quality Assurance

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 973 285 3100 Fax 973 285 1872

169 Albemarle Rd.
Newton, MA 02160

Nov. 26, 1997

Larry Christman, Ph.D.
Dir. Reg. Affairs & Quality Assurance
Alimenterics Inc.
301 American Road
Morris Plains, NJ 07950
By FAX: (973) 285-1872

Dear Dr. Christman,

I have calculated the Exact Confidence Intervals for both sensitivity and specificity that would result from a series of total sample sizes in your eradication study. I have assumed throughout that, as with your patients to date, [redacted] of the patients are positive by the gold standard. Further, that the observed sensitivity and specificity among the study patients are each [redacted] I calculated the Confidence Intervals using the current total sample size of [redacted] patients and the for the three sample sizes of [redacted] patients. The results are in the following table.

Total n	[redacted]
Gold pos:neg	
Sens. CI %	
Spec. CI %	

As you can see from the table, you should have already achieved the design goal of a width for the specificity CI of ±5%. However, due to the low number of patients who are gold standard positives at follow-up, you will not be able to achieve that goal with regard to sensitivity with the designed sample size. To do so would require continuing even beyond the point where [redacted] evaluable patients were enrolled.

Handout #1

From these numbers, it appears as if you have reached the point of diminishing returns and there is little to be gained by continuing the study to its designed sample size.

Sincerely Yours,

/S/

Elkan Halpern, PhD. D.

APPEARS THIS WAY
ON ORIGINAL

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 26 1997

Mr. Edward M. Basile
King and Spaulding
1730 Pennsylvania Avenue, N.W.
Washington, D.C. 20006-4706

RE: Application fee for NDA 20-900, ^{13}C-Urea Enriched under the Prescription Drug User Fee Act of 1992 (PDUFA)

Dear Mr. Basile:

This responds to your September 17, 1997 letter to Mr. Thomas Hassall of my staff concerning the assessment of an application fee under the PDUFA for an application that requires clinical data for approval for NDA 20-900, ^{13}C-Urea Enriched, which was submitted by Alimenterics, Inc. (Alimenterics) on August 8, 1997.

Alimenterics is applying for approval to market the LARA™ Breath Test System for detection of Helicobacter pylori in adult gastric mucosa. The system consists of the Laser Assisted Ratio Analyzer (LARA™), the PYLORI-CHEK™ Breath Test Kit containing breath collection apparatus and the drug, ^{13}C-Urea (100 mg). [redacted] is also provided for reconstitution of the drug to form a solution for oral ingestion.

By letters from the Office of the Commissioner dated June 21, 1993, January 12, 1995, and January 27, 1995, the Product Jurisdiction Officer, Amanda B. Pederson [now Amanda Bryce Norton] established the jurisdictional responsibilities for review of this combination drug/device product between the Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research (CDER). The letters also stipulated that the drug component, ^{13}C-Urea, would be reviewed and regulated under the new drug provisions of the Act (21 U.S.C. § 355), which requires a new drug application (NDA), and that the Prescription Drug User Fee Act requires an application fee for certain new drug applications.

An application for approval of a new drug under the Federal Food, Drug, and Cosmetic Act (FD&C Act) must meet the requirements of section 505, which include the submission of full reports of investigations made to show that the drug is safe and effective, or, for a generic drug, information to show that the conditions of use in the labeling for the new drug have been previously approved. Alimenterics' ^{13}C-Urea product does not meet the requirements for submission as an abbreviated new drug application under section 505(j) of the FD&C Act.

Designation of CDRH as the agency component with primary jurisdiction for review and regulation of the product is separate from the determination of the statutory provision under which each component of the combination will be reviewed and regulated. Such designation does not alter the statutory requirement for approval of a new drug under section 505.

Similarly, PDUFA does not differentiate 'human drug applications' that fall under the primary jurisdiction of one agency component from those reviewed under the primary jurisdiction of another component with respect to application fees.

With respect to the requirement for the review of clinical data for approval of NDA 20-900 for ^{13}C-Urea, you stated that its pharmacology and toxicology profiles and metabolism are well understood; that there are no significant safety issues in the doses being administered; that it has no therapeutic effect; and that there are no safety or therapeutic effectiveness issues. You said the only clinical effectiveness issues raised by the LARA™ Breath Test System relate to the sensitivity, specificity and negative and positive predictive values of the diagnostic device. This conclusion contradicts FDA's finding, as conveyed in Ms. Pederson's letters, that the ^{13}C -Urea component was a new drug subject to the new drug approval provisions of the FD&C Act. Indeed, the device alone would have no predictive value at all as a diagnostic test for Helicobacter pylori without the ingestion of the drug at a time and in an amount determined by clinical testing to yield a reliable result. Clinical data that define such conditions of use are required for approval of the NDA regardless of the Center in which the NDA is reviewed. While the NDA may not *physically contain* a copy of the clinical reports supporting the safety and effectiveness of ^{13}C -Urea in the LARA™ Breath Test System, such data are presumably incorporated into the NDA by reference to data submitted in the 510(k) applications. Under PDUFA, the amount of the fee is based upon whether clinical data are *required* for approval, not upon whether an application *contains* clinical data. Because FDA reviewers must review clinical data to approve the drug, NDA 20-900 is subject to the application fee defined under section 736(a)(1)(A)(i) of the PDUFA regardless of whether the review is conducted by CDER, by CDRH, or by a collaborative effort involving both centers.

We have determined, based on Alimenterics' application, the letters from the Office of the Commissioner, and the information in your September 17, 1997 letter, that there is no regulatory or scientific basis on which to conclude that NDA 20-900 does not require review of clinical data for approval or that the application is not subject to an application fee under the provisions of the PDUFA. Therefore, we have determined that the Fiscal Year 1997 application fee [redacted] was correctly assessed. If you have further questions with respect to the fee for this application, please contact Mr. Thomas Hassall, Mr. Michael Jones, or Ms. Joslyn Swann at (301) 594-2041.

Sincerely,

/S/

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

NDA 20-900

SECTION TWO

2.1 NDA Patent Filing Information

According to "Approved Drug Products with Therapeutic Equivalence Evaluations," Seventeenth Edition (1997), U.S. Patent No. 5140993 (exp. Aug. 24, 2009) is responsive to 21 U.S.C. § 355(b)(1)(F). See attached photocopy of page AD 60.

Alimenterics

NC
NEW CORRESP
ORIGINAL

January 12, 1998

Ms. Robin Anderson
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 827-2510

Subject: Response to Chemistry Reviewers Comments for NDA 20-900

Dear Ms. Anderson

Enclosed you will find three copies of our response to the chemistry reviewer's comments (dated November 14, 1997) for our NDA application 20-900. I have faxed an advance copy of this letter and our response to you and to Dr. Woody Dubois.

Respectfully,

C. Lawrence Christman, PhD
Director of Regulatory Affairs
and Quality Assurance

cc: Woody Dubois, Fax 301 594-5940
Janet Murnick, PhD

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 201 285 3100 Fax 201 285 1872

[redacted]

January 22, 1998

Dr. R. Craig Kammerer
Alimentaria, Inc.
301 America Road
Morris Plains, NJ 07950

Dear Dr. Kammerer.

This is to confirm that [redacted] is negotiating terms of a method and contract to try to assay C13 in C13 Urea.

[redacted]

Upon successful completion of the contract, [redacted] will carry out the assay procedure using the method development.

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours,

/S/

Alimenterics

January 23, 1998

Ms. Robin Anderson
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 594-5940

Subject: Clarification to Response Dated (01/12/98) - NDA 20-900

Dear Ms. Anderson:

Today, Dr. Salako and I talked about Alimenterics' latest response for NDA 20-900. This letter clarifies the three issues Dr. Salako and I discussed.

[redacted]

As requested, Alimenterics has set a release specification for pH. It applies to tests on all reconstituted urea samples from each lot of dispensed bulk drug substance and each stability test. Alimenterics will add the following acceptance criteria to its quality assurance testing for release of dispensed ^{13}C labeled urea and for stability testing:

- Measure the pH of reconstituted urea using the same method described in validation document 950011.
- Record the pH at 0, 12, 30, 60, 120, and 360 minutes (6 hours) after reconstitution.
- Using results from 5 samples, compute the mean pH for each time point.
- If the mean at 6 hours drops more than pH unit from the mean at time - reject the lot.

Alimenterics agrees the packet insert submitted with our response dated, January 19, needs revision. This was an early version of the packet insert which was submitted with our original 510K premarket notification application. Since then CDRH has requested revision. Alimenterics submitted a revised draft of our packet insert which corrects the structure for urea (page 4), changes the storage life to 20 months and changes the storage temperature recommendation.

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 973 285 3100 Fax 973 285 1872

These explanations document what Dr. Salako and I agreed to. If I can provide any additional information or clarification please call me.

Respectfully,

C. Lawrence Christman, PhD
Director of Regulatory Affairs
and Quality Assurance

cc: Janet Murnick, PhD
Woody Dubois, PhD Fax 301 594-5940

APPEARS THIS WAY
ON ORIGINAL

Alimenterics

February 9, 1998

Dr. Mark Goldberger, Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

BL

Subject: Revised Draft Labeling for NDA 20-900

Dear Dr. Goldberger:

I have enclosed a paper copy of our revised draft labeling for NDA application 20-900, which the FDA and Alimenterics agreed to on February 5, 1998, during a phone conversation with Dr. Woody Debois of CDRH. As requested we are submitting a paper copy along with a electronic file copy formatted using WP 6.1.

Ms. Robin Anderson indicated a debarment statement was missing from our original application. Please include the enclosed debarment statement with our application.

If I can provide any additional information, please contact me.

Respectfully,

Larry Christman

C. Lawrence Christman, PhD
Director Regulatory Affairs
and Quality Assurance

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 973 285 3100 Fax 973 285 1872

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Kathryn Gleason
Roberto Cuca
Morgan, Lewis & Bockius
1800 M Street
Washington, D.C. 20036-5869

MAR 06 1998

Re: Five Year Exclusivity for NDA # 20-586

Dear Ms. Gleason and Mr. Cuca:

I am writing in response to your letter of December 15, 1997 to Dr. Gary Chikami of the Division of Anti-Infective Drug Products regarding the five year exclusivity period that has been granted to your client Meretekdiagnostics, inc ("Meretek") for NDA # 20-586. This NDA is for the C^{13} urea drug component of a combination drug/device product used to detect the presence of *H. pylori* in the digestive tract. Your letter requested assurance that FDA will enforce Meretek's exclusivity against any 505(b)(2) application for a drug product that contains C^{13} urea. I have also considered the points you raised on behalf of your client at a February 12, 1998 meeting with the Division, and in a February 20, 1998 letter to Elizabeth Dickinson in FDA's General Counsel's Office. You have requested FDA assurance as to its actions with respect to a particular NDA. As you know, the agency will not disclose the existence of an application before an approvable letter is sent to the sponsor. 21 CFR 314.430. Therefore, I cannot address your concerns with respect to a specific application. I can, however, provide information regarding the scope and nature of the new chemical entity exclusivity Meretek has been granted.

Certain exclusivity provisions under the 1984 Waxman-Hatch Amendments to the Federal Food, Drug, and Cosmetic Act prohibit FDA from accepting for five years a 505(b)(2) application or an application under 505(j) for a drug that contains the same active moiety as a drug product containing a new chemical entity. 21 U.S.C. 355(c)(3)(D)(ii) & (j)(4)(D)(ii); and 21 CFR 314.108. This exclusivity protection does not prohibit FDA from accepting and approving a "full" NDA submitted under 505(b)(1) for a drug that contains the same active moiety, where the sponsor of the second application either has obtained a right of reference to or has conducted or sponsored all of the studies necessary to the approval of the NDA.

Your position is that the Meretek NDA for C^{13} urea was a 505(b)(2) application. After review of the Meretek NDA and additional consideration of the issues raised in your letter, the Division has determined that the Meretek NDA was not a 505(b)(2) application, because all of the investigations relied upon for approval were conducted by or for Meretek. Although the Meretek NDA submissions for C^{13} urea included published studies to support the pharmacology/ toxicology component of the application, such submissions were not essential for approval. As you correctly note, the August 4, 1995 preclinical/clinical safety review of the Meretek NDA stated that the Meretek submission included reprints of articles from the scientific literature addressing the toxicity of urea, and the reviewer summarized the conclusions of such submissions. However, the fact that this literature was submitted and reviewed is not dispositive

of the question of whether, without these submissions, the application could have been approved. During the course of a review the Agency will evaluate a great deal of information submitted by the Sponsor. Not all of the data will ultimately be found essential to the approval decision.

I have reviewed the "Recommendations for NDA Requirements for Urea Breath Tests" sent to you by the agency in February, 1995. This list of recommendations was intended as guidance to Meretek in preparing its NDA; such recommendations were not a determination of what specific data would ultimately be relied upon for approval of the application. An informal communication with FDA employees prior to submission of the NDA is not determinative of what specific data will be relied upon by the agency for approval.

In some cases, at the time of approval of an NDA a specific determination is made as to whether certain information or data submitted by the sponsor was essential to approval of an application. Specifically, this analysis is undertaken when an NDA sponsor requests three years of market exclusivity under Sections 505(c)(3)(D)(iii & iv) and (j)(4)(D)(iii & iv), and the agency must determine whether clinical investigations conducted by the sponsor are essential to approval. At the time of approval of the Meretek NDA, no such determination was made as to whether the pharmacology/toxicology data submitted for review was necessary for approval.[1]

In the case of urea, our review of the issue has determined that although the literature reprints submitted by Meretek were informative, they were not essential for approval of the single dose urea product. This division's Pharmacology/Toxicology Team Leader, in consultation with Dr. Joseph DeGeorge, Associate Director for Pharmacology and Toxicology, CDER, has concluded that because urea is present naturally in the human body in amounts far in excess of those used in the single dose breath test, and because the dose of urea (125 mg) and the route of administration in the Meretek product are consistent with GRAS usage under 21 CFR 184.1923, pharmacology and toxicology data were not necessary for approval of the Meretek NDA. Therefore, because the only published studies submitted in the NDA were not relied upon for approval, the Meretek NDA was a "full" NDA, rather than a 505(b)(2) application.

I am aware that your letter was not initially intended to raise the issue of whether Meretek's application was itself a "full" NDA or a 505(b)(2) application, but rather to address the scope and effect of Meretek's exclusivity. Nonetheless, in order to respond to your inquiry, it has been necessary to determine whether an application for a C^{13} urea breath test is required to contain pharmacology and toxicology data for approval.

---

[1] The status of the Meretek NDA as a "full" NDA or a 505(b)(2) NDA has no bearing on whether it is entitled to a new chemical entity exclusivity. You correctly note in your letter that both types of application are eligible.

If FDA were to conclusively determine that, as outlined in this letter, such data was not necessary for approval of the Meretek NDA, any NDA for a C^{13} urea breath test that utilizes a urea dose consistent with naturally occurring levels of urea and with GRAS usage also would not be required to submit pharmacology/and toxicology data for approval. Therefore, if the sponsor owned or had a right to all the other data in the NDA, the application would be classified as a "full" NDA, which could be accepted and approved notwithstanding Meretek's new chemical entity exclusivity.

This letter is informal correspondence and does not constitute final agency action. A final administrative decision on the issues you have raised may be obtained by submitting, in the form of a citizen petition pursuant to 21 CFR 10.30, a request for FDA to determine whether pharmacology and toxicology data was essential to approval of Meretek's NDA, and therefore also would be essential to approval of a similar application. Given the attention that has already been given to this issue, the agency would be in a position to rule on your citizen petition in an expeditious manner.

Please don't hesitate to contact me or Elizabeth Dickinson in the Office of the Chief Counsel (301-827-1126) if you have additional questions.

Sincerely,

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens
And Immunologic Drug Products

...EARS THIS WAY
ON ORIGINAL

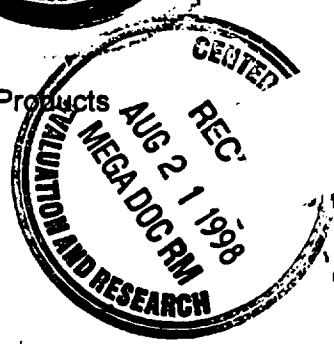
Alimenterics

BC

ORIG AMENDMENT

ORIGINAL

March 12, 1998



/S/
08/07/98
Noted & see the review.

Ms. Robin Anderson
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 827-2510

Subject: Amendment to - NDA 20-900

Dear Ms. Anderson:

Following the advice of the pre-approval inspector from the FDA, I am submitting the following information which amends Alimenteric's NDA application – NDA 20 – 900. The information falls into three categories: notification of change in manufacturing facility, revised plan for assaying ^{13}C enrichment of the bulk drug substance and the addition of an alternate test laboratory.

Alimenterics has agreed to do ^{13}C enrichment testing on samples of dispensed drug prior to final release. Although the bulk drug manufacturer [redacted] does this test and certifies it on a COA which accompanies each order, Alimenterics agreed to confirm their test results. In our letter dated January 13, 1998, we proposed to use [redacted] to do these tests. Unfortunately, [redacted] quote was prohibitively high. Enclosed you will find a copy of the report [redacted] which documents our efforts to locate a contact laboratory for ^{13}C enrichment testing. We will continue to search for a contact laboratory capable for performing this test, but none is available now. As an alternative, we propose to send blinded samples back to [redacted] and use their test results as our acceptance criteria. A protocol for the test methods is attached [redacted]

In our original NDA, we listed [redacted] as the site of manufacturing and testing [redacted] This site was used to dispense and assemble test kits used for clinical trials. This facility is too small for full scale production runs. We have moved the drug dispensing, kit assembly, quality assurance analysis testing and stability sample storage to an adjacent building. These activities will be done at [redacted] Enclosed is a copy of an amendment to page 41 of NDA 20-900. Attached is a floor plan for [redacted] which shows the kit manufacturing area, the urea dispensing room, the control gas dispensing room, the chemistry laboratory, the location of the environmental chambers used for storing stability samples and various quality assurance control areas. The urea dispensing room is a [redacted]

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 973 285 3100 Fax 973 285 1872

controlled environment and the kit manufacturing area

Enclosed is a revised copy of page 41 of NDA 20-900 which gives the complete address of the kit production facility and adds an alternate contact test laboratory.

Respectfully,

C. Lawrence Christman, PhD
Director of Regulatory Affairs
and Quality Assurance

cc: Janet Murnick, PhD
Woody Dubois, PhD Fax 301 594-5940

APPEARS THIS WAY
ON ORIGINAL

Alimenterics

BC

ORIG AMENDMENT

ORIGINAL

July 22, 1998

Ms. Robin Anderson
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 827-2520

Subject: Amendment to - NDA 20-900

Dear Ms. Anderson:

Alimenterics has added additional contract laboratories for maintaining stability samples under controlled environmental conditions, testing reference materials used for analytical assays and for quantitating the amount of impurities in specimens. Enclosed is a revised copy of page 41 of NDA 20-900 which gives the complete list of locations for manufacturing and testing the Pylori-Chek Breath Test Kit.

Respectfully,

Larry Christman

C. Lawrence Christman, PhD
Director of Regulatory Affairs
and Quality Assurance

cc: Regina Brown, Pre-approval Inspection Coordinator
Ben Stein, President Alimenterics
Judi Smith, Corporate Regulatory Affairs and Quality Assurance

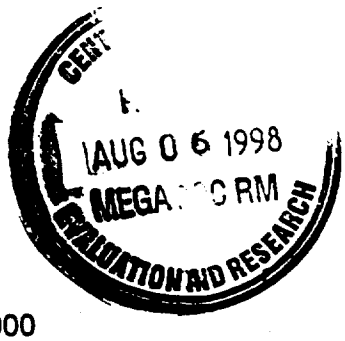
Alimenterics

NC
NEW CORRESP
ORIGINAL

August 5, 1998

Ms. Robin Anderson
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 827-2520



Subject: Copy of Response to FDA 483 Observations – NDA 20-900

Dear Ms. Anderson:

I have enclosed two copies of our response to an FDA 483 observations report which Alimenterics received on June 9, 1998. The report was generated after a pre-approval inspection for our NDA application. Also, I have sent a copy to Ms. Regina Brown, the pre-approval inspection coordinator for our district and a copy to Ms. Lisa Hall the FDA inspector who conducted the inspection of our facility. Our response documents the corrective actions taken and planned, which will resolve issues raised during the inspection. Please consider this information when CDER staff meets on August 12, 1998, to decide the status of our NDA.

Alimenterics' response demonstrates the company's commitment to satisfy the FDA's concerns over our quality system, test method validations and equipment qualifications. Alimenterics has undergone major changes, including a change in senior management. The company has invested approximately [redacted] in building modifications to better control the environment within the kit production area and our storage areas. We have retained the services of consultants and have hired key employees. These investments demonstrate management's commitment to resolve the FDA's concerns.

Since the last inspection, the company has taken steps to improve its Quality Systems. The company has retained the services [redacted] a firm offering compliance and validation regulatory consulting in the pharmaceutical and medical device industry. Consultants from the firm will review our quality system procedures and records, conduct a mock pre-inspection audit and advise us on how to correct any deficiencies or weaknesses. These actions will help facilitate the FDA's re-inspection of our facility. Recently, the company has added key personnel. Alimenterics as hired a kit production supervisor and a quality assurance manager with over 5 years experience in the pharmaceutical industry. The company has provided employees with Good Manufacturing Practices Training.

Alimenterics has performed additional work to validate its analytical methods. Data submitted with this response support Alimenterics' belief that our [redacted] urea

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 973 285 3100 Fax 973 285 1872

has sufficient accuracy, precision and robustness to quantify the identity, strength, purity and quality of our drug product. Failing to meet a capacity factor specification is its major limitation. While Alimenterics would prefer to use its current method, if the FDA decides our current method is unsatisfactory, Alimenterics will agree to continue to search for a column with the same performance characteristics but a higher capacity factor.

Alimenterics has taken steps to improve its process for dispensing bulk drug substance into single dose containers. These plans include making building modifications to better control the environmental in the dispensing and manufacturing areas, revising procedures for dispensing operations, performing a re-qualification of the dispensing machine, training manufacturing personnel in the new procedures and conducting a revalidation of the dispensing process on three manufacturing lots. This work is scheduled for completion by September 30, 1998. After implementing this improvement program, the company will have objection evidence its process for dispensing ^{13}C urea is well controlled.

Our response and the attached supporting material demonstrate Alimenterics' commitment to resolve concerns the FDA has over our quality systems, our analytical methods and our dispensing process. Senior management is committed to taking whatever corrective actions are necessary to satisfy the FDA's concerns.

The company will await the Agency's decision on the status of our New Drug Application and its decision about the adequacy of our [redacted]

Respectfully,

Larry Christman

Larry Christman, PhD
Director of Regulatory Affairs and Quality Assurance

APPEARS THIS WAY
ON ORIGINAL

AUG 2 6 1998

NDA 20-900

Alimenterics, Inc.
Attention: Larry Christman, PhD
Director of Regulatory Affairs and Quality Assurance
301 American Road
Morris Plains, NJ 07950

Dear Dr. Christman:

Please refer to your new drug application (NDA) dated August 8, 1997, accepted for filing on August 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the PYLORI-CHEK Breath Test Kit containing ^{13}C-Urea 100 mg.

We acknowledge receipt of your submissions dated October 27, 1997, January 12, February 9, March 12, April 14, July 22 and August 5, 1998. The user fee goal date for this application is August 26, 1998.

We have completed our review and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspection of your facility as well as the contract laboratories is required before approval of this application can be granted under the GMP requirements of 21 CFR 210. Specifically, the following is required for approval:

[redacted]

Your procedure of resubmitting the samples in a blinded manner to [redacted] the supplier of bulk drug substance, is acceptable for the short term while you attempt to locate a suitable laboratory for the isotope abundance assay. However, please be advised that a phase IV commitment to develop and validate an in-house method or to identify a suitable testing laboratory will be required for approval.

Within 10 days after the date of this letter, you are required to amend the application, notify us of

your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Robin Anderson, Project Manager, at (301) 827-2127.

Sincerely,

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Alimenterics

ORIGINAL

August 28, 1998

Dr. Mark J. Goldberger, MD, MPH
Director, Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 827-2520

Subject: Response to Non-Approval Letter for NDA 20-900, dated August 27, 1998

Dear Dr. Goldberger:

Alimenterics has received your letter of Non-Approval for the company's NDA for our Pylori-Chek Diagnostic Breath Test Kit. The FDA has set conditions the company must meet before the Agency will consider our application for approval.

As discussed in our response to 483 observations dated August 5, 1998, Alimenterics has a plan for satisfying all issues the FDA investigator raised and expects to complete these activities by the end of September. The company and a group of consultants it has retained are reviewing and improving our Quality Systems and retraining employees. The training included:

Alimenterics requests the FDA inspect the suppliers mentioned in its Action Letter. As noted below, the FDA has inspected some of these suppliers. Previous inspections may satisfy the inspection requirements for our NDA.

Passed FDA Inspection, Last Inspected, April 11, 1996
Passed FDA Inspection, Last Inspected, June 3, 1998
Passed FDA Inspection, Last Inspected, Feb. 21, 1996
Not FDA Inspected

After the conference call with the FDA on August 20, 1998, Alimenterics began a program to develop the use of a new with a capacity factor greater than 2 or a new analytical method. Preliminary results suggest one of nearly a dozen new the company is investigating for the may meet the capacity factor acceptance criteria. The company plans additional work to check that this meets all performance criteria.

Alimenterics will use the blinded sample method for ^{13}C enrichment testing but will continue to search for alternate methods or suppliers.

Alimenterics Inc.
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When results are available from analytical methods development and dispensing operations validation and when quality systems improvements are complete, the company intends to amend its application. We expect to file the amendment before November 2, 1998. Alimenterics requests the FDA not withdraw the company's application. When the company completes these activities, the company will request another Pre-Approval Inspection. Alimenterics will not market its product without the FDA's written approval of its NDA.

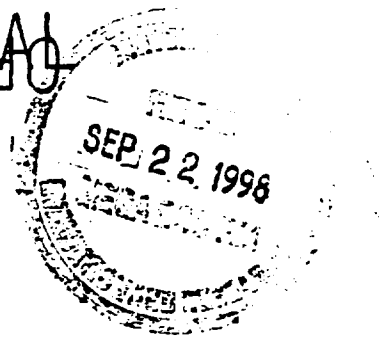
Respectfully,

Larry Christman, PhD
Director of Regulatory Affairs and Quality Assurance

Cc: Regina Brown, Pre-Approval Inspection Coordinator
Judith Smith, Worldwide Regulatory Affairs and Quality Systems, MSG

APPEARS THIS WAY
ON ORIGINAL

Alimenterics ORIGINAL



NEW CORRES

NC

September 21, 1998

Ms. Robin Anderson
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 827-2520

Subject: Remove Supplier [redacted] from NDA 20-900

Dear Ms. Anderson:

In amendment dated July 22, 1998, Alimenterics added additional contract laboratories to NDA 20-900, including [redacted] located at the following address:

[redacted]

This contract laboratory was listed as providing the following services: [redacted] While Alimenterics listed several services, the company only used [redacted] to perform [redacted] In an action letter from the FDA dated August 26, 1998, the FDA added certain requirements for approval, including that [redacted] pass an FDA inspection.

During recent discussions with [redacted] Alimenterics learned there was a misunderstanding between the two companies. While Alimenterics thought the company received cGMP compliant and validated test results, apparently that was not the case. As a result, Alimenterics is searching for another supplier who can provide these services. The company has found an alternate supplier but plans an audit to qualify them. Our Quality Assurance Department expects to complete the audit within two weeks. Once Alimenterics has qualified a new supplier, the company will inform the FDA.

Alimenterics Inc.
118 American Road Morris Plains, NJ 07950 Phone: 973.285.3100 Fax: 973.539.5493

Please remove [redacted] from Alimenterics' NDA and cancel the inspection of their facility.

Respectfully,

C. Lawrence Christman, PhD
Director of Regulatory Affairs
and Quality Assurance

cc: Regina Brown, Pre-approval Inspection Coordinator
Ben Stein, President Alimenterics
[redacted]

APPEARS THIS WAY
ON ORIGINAL

Alimenterics

December 11, 1998

Ms. Regina T. Brown
Pre-Approval Program Manager
Food and Drug Administration
120 North Center Drive
North Brunswick, NJ 08902

Fax No. 732 940-8936

Subject: Preapproval Inspection June 9, 1998 – NDA 20-900

Dear Ms. Brown:

We are writing in response to your letter dated June 10, 1998, in which you recommended the company's application remain in a withhold status. Since then, Alimenterics has undertaken a major improvement program focused on our quality systems, validating our dispensing process and developing a stability indicating assay which meets all the FDA requirements. Enclosed you will find highlights of this program and a discussion of specific actions the company has taken in response to each 483 observation.

Alimenterics believes the company is now in substantial compliance with cGMPs and requests you schedule another pre-approval inspection. Our decision that the company is ready to host another inspection was based on our identified Quality System improvements and on the evaluation of consultants. We believe the improvements will lead to a successful FDA inspection.

Since gaining marketing approval is a critical step for the future of the company, Alimenterics appreciates your help in expediting the FDAs re-inspection.

Respectfully,

Larry Christman, PhD
Director of Regulatory Affairs
and Quality Assurance

Judith J. Smith
Corporate Director,
Regulatory Affairs and Quality Systems

cc: Lisa Hall, Inspector
Robin Anderson, CDER
Ben Stein, President Alimenterics

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 201 285 3100 Fax 201 285 1872

10 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

Alimenterics

December 14, 1998

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NC

Dr. Mark J. Goldberger, MD, MPH
Director, Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

RE: NDA 20-900 – Follow-up Status Report to "Not Approvable" Letter

Dear Dr. Goldberger,

The following information is provided to address the issues raised in the "Not Approvable" letter dated Aug 26, 1998:

- **Satisfactory inspection of [redacted] submitted to the NDA subsequent to the FDA inspection of the facilities listed in the original NDA.**

  As noted in our response dated August 28, 1998 to the "Not Approvable" letter, [redacted] was last inspected April 11, 1996 and [redacted] was last inspected Feb. 21,1996. Since that response, [redacted] was inspected by the FDA in September 1998 specifically for our NDA. They were notified on September 29, 1998 by the FDA NJ District Office of their successful completion of inspection.

  In addition, as was communicated to Ms. Robin Anderson in our letter dated September 21, 1998, we had a miscommunication with [redacted] This resulted in our pursuit of an alternate vendor to perform the needed [redacted] Their last inspection was August 1998. We hope these previous inspections will satisfy the inspection requirements for our NDA.

- **Satisfactory inspection of the Alimenterics facility. Specific deficiencies were listed in the inspection report (483) dated June 6, 1998.**

  As a result of the FDA inspection, Alimenterics reviewed all of its quality systems and identify several areas that needed strengthening. The company brought in several consultants to help with the task of preparing, implementing and auditing the improvements. We have worked very hard to address not only the issues identified in FDA 483 but the broader programs trended by these observations. We have made tremendous progress since the last inspection and believe we have addressed all of the observations. On December 11, 1998, we requested a reinspection by the district office.

Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 201 285 3100 Fax 201 285 18[illegible]2

- **Development and validation of a suitable [redacted] with a capacity factor of 2 or more. This method should be included in the release specification and stability protocol of ^{13}C-Urea. The current [redacted] validation data does not need to be submitted since you are required to develop a new method.**

Alimenterics has identified an [redacted] which has the system suitability requirements [redacted] established in the Center for Drug Evaluation and Research Reviewer Guidance "Validation of Chromatographic Methods", November 1994. The capacity factor as defined in the guid[redacted]

[redacted]

If you have any questions, please contact me at (973)285-3102 or by fax at (973)539-5493.

Sincerely,

Larry Christman, PhD
Director of Regulatory Affairs and Quality Assurance

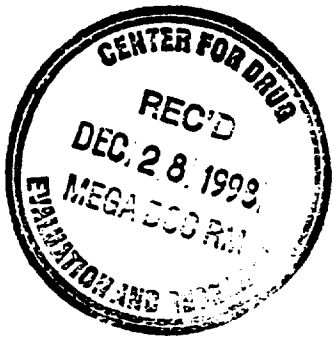
Cc: Regina Brown, Pre-Approval Program Manager
Judith Smith, Corporate Director
Ben Stein, President Alimenterics

___ pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

Alimenterics

BC

December 22, 1998



Ms. Robin Anderson
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 827-2520

Subject: Amendment to - NDA 20-900

Dear Ms. Anderson:

I have enclosed two copies of an amendment to NDA 20-900. The material and attachments are organized consistent with the organization of the original application. Section 5 - Full Address of the Facility for the Drug Product Manufacturing, Packaging and Stability Testing, Section 6 - Unexecuted Master Batch Production Record, Section 7 - Product Validation, Section 8 - Final Release Specifications and Analytical Methods for Final Release and Section 9 - Stability Test Results are amended.

In some cases, material with this amendment supercedes information submitted in earlier amendments. In those cases, I have noted the change.

In a letter to the FDA's local Pre-Approval Program Manager dated Dec 11, 1998, Alimenterics committed to sending the FDA additional information. This amendment satisfies this commitment.

Respectfully,

Larry Christman

C. Lawrence Christman, PhD
Director of Regulatory Affairs
and Quality Assurance

cc: Regina Brown, Pre-approval Inspection Coordinator
Ben Stein, President Alimenterics
Judi Smith, Corporate Regulatory Affairs and Quality Assurance

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Alimenterics Inc.
301 American Road Morris Plains, NJ 07950 Phone 201 285 3100 Fax 201 285 1872

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Alimenterics

ORIG AMENDMENT

ORIGINAL

January 13, 1999

Ms. Robin Anderson – Desk Copy
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Fax 301 827-2475

Subject: Amendment to NDA 20-900, dated December 22, 1998

Dear Ms. Anderson:

During a recent Pre-Approval Inspection, the FDA compliance inspector suggested Alimenterics clarify certain SOPs and reports submitted with the subject amendment. Subsequently, the company revised the following SOPs and issued addenda to the following reports:

Report Number	Title	Description of Clarification/Addition

A copy of these documents is included with this amendment.

Alimenterics Inc.
118 American Road Morris Plains, NJ 07950 Phone: 973.285.3100 Fax: 973.539.5493

In the subject amendment, the company found a few typographical errors which we would like to correct with this submission. Please replace the following pages from the subject amendment:

Page	Description of the Correction
9	In the subject amendment the reference to [redacted] was replaced with [redacted] in one place but not in the other.
112	Page 3 of Alimenterics Protocol #950077 was missing from the subject amendment. Please include page 112a with the subject amendment.

Respectfully,

C. Lawrence Christman, PhD
Director of Regulatory Affairs
and Quality Assurance

cc: Regina Brown, Pre-approval Inspection Coordinator
Ben Stein, President Alimenterics
Judi Smith, Corporate Regulatory Affairs and Quality Assurance

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 4 1999

To: File NDA 20-900

From: Mark J. Goldberger, M.D., M.P.H.

Subject: Division Director's memo regarding the approval of this NDA

The review of NDA 20-900 submitted by Alimenterics for the C^{13} urea component of a new diagnostic test for H. pylori was complicated by exclusivity concerns raised by Meretekdiagnostics who had a previous application approved for a similar product. These issues are summarized in my letter of March 5, 1998 (attached) to Meretek and revolve around the 505 (b)(2) application process, and in particular to the determination of whether information submitted as a part of a NDA is necessarily essential to the actual approval decision for that NDA. In this case, the Agency determined that some of the information submitted in the Meretek NDA; i.e., the toxicity information on C^{13} urea was not essential to the approval of that application. As a consequence, this approval did not preclude the Agency from accepting, reviewing and approving the Alimenterics application.

The approval was also delayed by problems in the results of the inspection at the Alimenterics manufacturing facility. These have now been resolved.

Hopefully this situation will have provided an opportunity to clarify some of the policy issues associated with the 505 (b)(2) process that will simplify the Agency approach to similar issues in the future.

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens
And Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Original NDA 20-900
HFD-590/Div. Files
HFD-590/R. Anderson
HFD-590/E. Frank
HFD-590/R. Hopkins
HFD-590/K. Hastings
Parklawn 671/GFC-1/E. Dickinson
HFD-007/W. Mitchell
HFD-604/D. Hare
HFD-160/E. Leutzinger
HFZ-440/D. Dubois
HFD-104/T. Hassall