CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-667

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.3.1.1 Patent Information

The undersigned declares that US Patent number 5,288,703 covers a method of increasing gut nutrient absorption by use of a combination of glutamine and growth hormone. This method is the subject of this application for which approval is being sought.

Patent number:	5,288,703 Issued February 22, 1994 Expiring February 22, 2012
Type of patent:	Method of use
Name of Patent Owner:	Brigham and Women's Hospital 75 Francis Street Boston, MA 02115 617-732-5500
Name of US Agent:	Sterne, Kessler, Goldstein & Fox
Address:	1100 New York Avenue, NW Washington, DC 20005 202-371-2600

US Patent number 5,288,703 claims the methods described in this application through the following specific claims:

Claim	Corresponding Label Text
1-3, 5, 7-13	**Indication:** Oral Glutamine is indicated in short bowel syndrome (SBS)
5, 7	**Dosage and Administration:** Oral Glutamine should be used as a cotherapy with rhGH (see Serostim® package insert for full prescribing information). Oral Glutamine should be administered in a divided daily dose of 30 g (5 g taken 6 times each day orally).

Allen Cato M.D., Ph.D.
President
Nutrition Restart Pharmaceutical, Inc.

Allen Cato

Signature

7-24-03

Date

1.3.1.2 Patent Certification

Paragraph IV Certification

I, Allen Cato, in accordance with 21 CFR § 314.50, certify that Nutrition Restart Pharmaceutical (NRP) has been granted an exclusive sublicense from Nutrition Restart Centers, L.P. (NRC), effective 09 February 1996, to practice the art described in US Patent number 5,288,703. NRC, in turn, has been granted an exclusive license to practice the art described in the patent from Brigham and Women's Hospital, Inc., the owner of this patent; the effective date of this latter license was 12 November 1992. The sublicense granted to NRP allows NRP to manufacture, use, and sell oral glutamine, for use in combination with growth hormone to increase gut nutrient absorption. This use of oral glutamine is the subject of this application for which approval is sought.

By:
Allen Cato M.D., Ph.D.
President
Nutrition Restart Pharmaceutical, L.P.

Allen Cato — Signature

7-24-03 — Date

EXCLUSIVITY SUMMARY FOR NDA # 21-667 SUPPL # N/A

Trade Name: NutreStore™
Generic Name: Oral Glutamine

Applicant Name: Cato Holdings, Inc.(US Agent for Nutritional Restart Pharmaceutical, L.P.)
HFD # 180

Approval Date If Known: June 10, 2004

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 question about the submission.

a) Is it an original NDA?
YES /X / Type 1 NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

---

d) Did the applicant request exclusivity?

YES /___/ NO /X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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 / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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?

YES / / NO /___/ Explain:

YES // NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

Investigation #1
YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2
YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO / /

If yes, explain

{See appended electronic signature page}

Tanya Clayton
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Robert L. Justice, M.D., M.S.
Division Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc: Original NDA-DFS
HFD-93 Mary Ann Holovac

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/s/

Tanya Clayton
6/10/04 11:50:49 AM

Robert Justice
6/10/04 11:53:25 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 21-667 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: August 12, 2004 **Action Date:** AP-June 10, 2004

HFD-180 **Trade and generic names/dosage form:** Glutamine Powder for Oral Solution

Applicant: Nutritional Restart Pharmaceutical, L.P. c/o Cato Research **Therapeutic Class:** Misc. GI

Indication(s) previously approved: Yes, NDA 21-597, December 1, 2003

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of short bowel syndrome

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A. (Included in the approval letter).**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

No pediatric data, no waiver request, no deferral request.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☒ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): _____

f studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Project Manager

cc: NDA
HFD-950/Grace Carmouze
(revised 9-24-02) FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-950
301-827-7777

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/s/

Tanya Clayton
6/9/04 01:37:32 PM

1.3.1.3 Debarment Certification

Nutritional Restart Pharmaceutical, L.P. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Allen Cato M.D., Ph.D.
President
Nutrition Restart Pharmaceutical, L.P.

Allen Cato
Signature

7-24-03
Date

MEMORANDUM

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

DATE: June 10, 2004

FROM: Julie Beitz, MD

SUBJECT: Deputy Office Director Memo

TO: NDA 21-667 Nutrestore (L-glutamine powder for oral solution);
Nutritional Restart Pharmaceutical, LP

This memo documents my concurrence with the Division of Gastrointestinal and Coagulation Drug Product's recommendation for approval of Nutrestore (L-glutamine powder for oral solution), indicated for the treatment of short bowel syndrome in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication. L-glutamine is an essential amino acid and is currently available as a dietary supplement and as a component of medical foods. On March 6, 1995, the Agency determined that L-glutamine qualified for orphan drug designation for use with human growth hormone in the treatment of short bowel syndrome (i.e., nutrient malabsorption from the gastrointestinal tract resulting from an inadequate absorptive surface). Evidence of L-glutamine effectiveness is based on a randomized, double-blind, controlled study conducted by Nutritional Restart Pharmaceutical, LP, in collaboration with Serono, Inc. This same study provided evidence of effectiveness for Serono's recombinant human growth hormone product, Zorbtive [somatotropin (rDNA origin) for injection]. Serono's NDA 21-597 for Zorbtive was approved on December 1, 2003.

The study randomized 41 patients with short bowel syndrome who were dependent on intravenous parenteral nutrition (IPN) to one of 3 treatment arms: (1) recombinant human growth hormone (rh-GH) 0.1 mg/kg/day s.c. for 4 weeks plus glutamine 30 g/day orally for 16 weeks, (2) rh-GH 0.1 mg/kg/day s.c. for 4 weeks plus a placebo for glutamine orally for 16 weeks, or (3) rh-GH placebo for 4 weeks plus glutamine 30 g/day orally for 16 weeks. All treatment arms received a specialized oral diet. The primary efficacy endpoint was change in weekly total IPN volume during weeks 2 to 6. Total IPN volume included IPN, supplemental lipid emulsion, and intravenous hydration fluid. The decrease in total IPN volume over the specified period was 7.7 L/wk for the co-therapy of rh-GH plus glutamine vs. 5.9 L/wk for rh-GH alone ($p= 0.023$), suggesting a glutamine effect. A decrease of 3.8 L/wk was observed for glutamine alone. The treatment effect was maintained for the entire 16 week treatment period. These findings support approval for use of L-glutamine at a dose of 5 grams orally 6 times daily for 16 weeks as co-therapy with rh-GH for the treatment of short bowel syndrome patients receiving a specialized oral diet.

Safety
The most common adverse events reported were gastrointestinal events typically observed in patients with short bowel syndrome receiving intravenous parenteral nutrition. Hepatic and renal function should be closely monitored in patients with short bowel syndrome receiving IPN and co-therapy with L-glutamine and rh-GH, particularly those with underlying hepatic or renal dysfunction.

Drug Interactions
Formal drug-drug interaction studies have not been performed.

Special Populations
The safety and effectiveness of L-glutamine in pediatric patients have not been established. In the randomized, controlled study, only 8 patients were enrolled who were 65 years or older, so it was not possible to conclude that older patients respond differently from younger patients.

Tradename Review
The proposed tradename "Nutrestore" is acceptable.

Phase 4 Studies
There are no phase 4 study commitments for this product. DGCDP will recommend that the sponsor develop a patient package insert post-approval.

/S/

Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
6/10/04 12:58:57 PM
DIRECTOR

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 10, 2004

To: Kevin Barber, Ph.D., R.A.C., Director of Regulatory Affairs	**From:** Tanya Clayton, B.S.
Company: Cato Research	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 919-361-2290	**Fax number:** 301-443-9285
Phone number: 919-361-2286	**Phone number:** 301-827-4005

Subject: NDA 21-667 Approval Letter

Total no. of pages including cover: 14

Comments:
Attached please find the approval letter for NDA 21-667, NutreStore.

Best regards.

Division Director Summary Review of a New Drug Application

NDA: 21-667
Drug: Nutrestore™ (L-glutamine powder for oral solution)
Applicant: Nutritional Restart Pharmaceuticals, L.P.
Date: June 3, 2004

This new drug application seeks approval of L-glutamine powder for oral solution for the following indication: "Oral glutamine is indicated in short bowel syndrome (SBS) as a

The application is supported by a single, randomized, controlled, 3-arm, double-blind, parallel-group clinical study designed to evaluate the efficacy and safety of recombinant human growth hormone (rh-GH) and oral glutamine as a cotherapy in patients with short bowel syndrome (SBS) who were dependent on intravenous parenteral nutrition (IPN) for nutritional support. The study was previously used to support the approval of Zorbtive® [somatropin (rDNA origin) for injection] for the treatment of SBS (see Division Director Summary Review of NDA 21-597). The primary endpoint was the change in weekly total IPN volume, defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid. The secondary endpoints were the change in weekly IPN caloric content and the change in the frequency of IPN administration per week.

All subjects received a specialized oral diet (SOD) for the duration of the study. Following a two-week stabilization period, patients were randomized 2:2:1 to treatment with rh-GH 0.1 mg/kg/day S.C. for four weeks plus glutamine placebo orally for 16 weeks [Group A (N=16)], to rh-GH 0.1 mg/kg/day for four weeks plus glutamine 30 g/day orally for 16 weeks [Group B (N=16)], or to rh-GH placebo for four weeks plus glutamine 30 g/day orally for 16 weeks [Group C (N=9)]. The results are shown on the next page in Table 1 from the proposed package insert.

For this application the comparison of interest is Group B (rh-GH plus glutamine) to Group A (rh-GH plus placebo). For the primary endpoint of total IPN volume (L/wk), at week 4 the mean change from baseline was -7.7 for Group B and -5.9 for Group A (p=0.023).

The persistence of treatment effect from week 2 to week 18 is shown in Table 2 on the next page. The change in weekly IPN volume was -7.2 for Group B and -5.9 for Group A. Although these data support that the treatment effect is maintained for 16 weeks, the efficacy of oral glutamine beyond 16 weeks of treatment has not been adequately studied.

Table 1

Results for Endpoints after 4 weeks of Treatment

	Group A rhGH + SOD [1]	Group B rhGH + SOD[GLN] [1]	Group C SOD[GLN] [1]
Total IPN volume (L/wk)			
Mean at Baseline	**10.3**	**10.5**	**13.5**
Mean Change	**-5.9**	**-7.7*** **	**-3.8**
Treatment differences (with GLN)	-2.1*	-3.9**	
Total IPN Calories (kcal/wk)			
Mean at Baseline	**7634.7**	**7895.0**	**8570.4**
Mean Change	**-4338.3**	**-5751.2**	**-2633.3**
Treatment differences (with GLN)	**-1705.0**	**-3117.9**	
Frequency of IPN or SLE (days/week)			
Mean at Baseline	**5.1**	**5.4**	**5.9**
Mean Change	**-3.0**	**-4.2**	**-2.0**
Treatment differences (with GLN)	**-1.0**	**-2.2**	

[1] SOD[GLN] = Specialized Oral Diet supplemented with Glutamine ; rhGH + SOD = Human Growth Hormone plus Specialized Oral Diet; rhGH + SOD[GLN] = Human Growth Hormone plus Specialized Oral Diet supplemented with Glutamine

*** p = 0.043, treatment comparison between rhGH + SOD versus SOD[GLN]**

**** p <0.001, treatment comparison between rhGH + SOD[GLN] versus SOD[GLN]**

*****p= 0.023, treatment comparison between rhGH + SOD[GLN] versus rhGH+SOD**

Table 2

Persistence of Treatment Effect

Change in IPN Volume, Calories, and Frequency Week 2 to Week 18 ITT Population			
Endpoint	**Group A*** [n = 16]	**Group B*** [n = 16]	**Group C*** [n = 9]
Change in weekly IPN Volume (L/wk)	-5.9	-7.2	-4.7
Change in weekly IPN Calories (kcal/wk)	-3522.2	-5347.3	-2254.0
Change in weekly IPN frequency (days/wk)	-2.9	-3.9	-1.9

GROUP A: rh-GH + SOD for 4 weeks followed by SOD for 12 weeks.
GROUP B: rh-GH + SOD [GLN] for 4 weeks followed by SOD [GLN] for 12 weeks.
GROUP C: rh-GH placebo + SOD[GLN] for 4 weeks followed by SOD[GLN] for 12 weeks.

Adverse events during the 4 week treatment period occurred in 100% of the rh-GH plus glutamine and rh-GH treatment groups and in 89% of the glutamine treatment group.

However, baseline signs and symptoms (BSS) were reported in 88% in each of the rh-GH groups and in 78% of the glutamine group. The most common adverse events were general, GI system, musculoskeletal, and resistance mechanism disorders. Peripheral and facial edema and arthralgias were clearly more common in the rh-GH arms. During weeks 5-16 adverse events were reported in 81% of the rh-GH plus glutamine group, 80% of the rh-GH group and 78% of the glutamine group. The most common adverse events were GI system disorders and resistance mechanism disorders. Many of the adverse events in both treatment periods may be related to the patients' short bowel syndrome or their parenteral nutrition.

Statistical Review and Evaluation

The statistical review by Dr. Dionne Price concluded that "There existed a decrease in IPN utilization over the treatment duration of 3.8L, 5.9L, and 7.7L among the glutamine, Zorbtive, and cotherapy groups, respectively. The unadjusted analysis yielded a significant reduction in total IPN volume when comparing Zorbtive alone and the cotherapy of Zorbtive and glutamine. The p-value for this comparison was 0.023. The result suggested a glutamine effect. The evidence indicated statistical support favoring glutamine as an add-on therapy to Zorbtive for the treatment of short bowel syndrome."

Division of Scientific Investigations

No new inspections were requested. The clinical study sites for this trial were inspected during the review of NDA 21-597 and were found to be acceptable.

Pharmacology/Toxicology Review

The Pharmacology/Toxicology Review by Dr. Ke Zhang recommended the following:

1) From a preclinical standpoint, approval of oral glutamine is recommended for short bowel syndrome as a cotherapy with recombinant human growth hormone for 4 weeks followed by additional 12 weeks with glutamine alone to reduce or eliminate the requirement for parenteral nutrition and to increase gut absorption of nutrients.
2) Labeling should be revised as recommended.

Chemistry Review

The Chemistry Review by Maria Ysern, MSc. Stated that "This NDA can be approved pending the resolution of the following issues:

1) Since all the information is in the related DMFs, the applicant needs to include in the NDA the Final specifications for the Drug Substance and the Drug Product.
2) The following changes to the label:

a. Under Dose and Administration:

b. Under Storage and on the labels: the statement should read: '(Glutamine Powder for Oral Solution) should be stored at 25°C(77°F) with excursions allowed to 15-30C (59-86F). [See USP Controlled Room Temperature].
c. The sponsor should apply for an NDC number if it has not already done so.

3) Include a specification for reconstitution time/dissolution in the drug product specification table based on your test data."

According to the Chemistry Team Leader, Dr. Liang Zhou, the applicant's response to these issues is currently under review.

Establishment Evaluation Request

All of the Establishment Evaluation Requests were acceptable.

Clinical Pharmacology and Biopharmaceutics Review

The Clinical Pharmacology and Biopharmaceutics Review by Dr. Sue Chi Lee stated that "From the Clinical Pharmacology and Biopharmaceutics standpoint, the application is acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and Agency regarding the language in (the) package insert."

DMETS Consultation

In their consultation of April 1, 2004, DMETS had no objections to the use of the proprietary name, Nutrestore™ from a safety perspective but recommended label and labeling revisions to minimize potential errors with use of the product.

DDMAC Memorandum

The DDMAC memorandum of March 23, 2004 included recommended labeling changes that were considered during labeling discussions.

Discussion

While this application is supported only by the results of a single two-center, randomized, controlled clinical trial, it is the largest randomized study reported in SBS.
Although one of the two centers contributed only 3 patients, the results of the study are statistically robust and the outcomes of the primary and secondary endpoints are internally consistent.

Regulatory Action

The application should be approved when the chemistry deficiencies have been adequately addressed.

{see appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
6/3/04 06:15:14 PM
MEDICAL OFFICER

ADMINISTRATIVE REVIEW OF NDA ACTION PACKAGE
OFFICE OF DRUG EVALUATION III

NDA: 21-667
Drug: Oral Glutamine
Classification: 1 S
Sponsor: Nutritional Restart Pharmaceuticals
Project Manager/CSO: Tanya Clayton

Reviewer: Bronwyn Collier, ADRA ODE III
Review Date: June 2, 2004

Review Cycle 1
Date Submitted: August 8, 2003
Date Received: August 11, 2003
Goal Date: June 11, 2004
Proposed Action: Approval

	STATUS	COMMENTS
ACTION LETTER	draft	
EXCLUSIVITY CHECKLIST	draft	
DEBARMENT STATEMENT	verified	
PEDIATRIC PAGE	draft	
TRADE NAME REVIEW	acceptable	
DSI AUDITS	acceptable	
FACILITY INSPECTIONS	acceptable	

REVIEWS	STATUS	COMMENTS
DIV. SUMMARY REVIEW	pending	
CLINICAL	completed	
SAFETY UPDATE	completed	Included in clinical review.
FINANCIAL DISCLOSURE	completed	Included in clinical review.
STATISTICAL	completed	
BIOPHARM	completed	
CMC	completed	
EA	completed	Addressed in CMC review.
MICRO (validation of sterilization)	N/A	

STABILITY (stats)	completed	Included in CMC review.
PHARM/TOX	completed	
CAC (stats)	N/A	
CAC/ECAC REPORT	N/A	

Labeling: Revised draft sent to sponsor–final wording under negotiation.
Postmarketing Commitments: none
Advisory Committee Meeting: none

Comments:
1. Pending reviews/addendums and docs in draft (e.g., exclusivity checklist, peds page) need to be complete prior to taking an action.

2. DMETS had several comments on the immediate container and carton labels. Status of comments needs to be documented. Submission of revised immediate container and carton labels pending.

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/s/

Bronwyn Collier
6/2/04 12:27:39 PM
CSO

emographic Worksheet

n Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-667 **Submission Type:** NME **Serial Number:** 000

lations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	12	All Females	29	Females >50	
Age:	0-≤1 Mo.	0	>1 Mo.- ≤2Year	0	>2-≤12	0
	12-16	0	17-64	33	≥65	8
Race:	White	32	Black		Asian	
	Other	9				

er-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☐ Yes	☒ No	☒ Inadequate #'s	☐ Disease Absent
Safety	☐ Yes	☒ No	☒ Inadequate #'s	☐ Disease Absent

Was gender-based analysis included in labeling?	
Yes	No
☐	☒
☐	☒

s a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

f the analysis was completed, who performed the analysis ☐Sponsor ☐FDA

Based Analyses *(Please provide information for each category listed below)*

ory	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☐ Yes	☒ No	☒ Inadequate #'s	☐ Disease Absent
Safety	☐ Yes	☒ No	☒ Inadequate #'s	☐ Disease Absent

Was age-based analysis included in labeling?	
Yes	No
☐	☒
☐	☒

s a dosing modification based on age recommended in the label? ☐ Yes ☒ No

f the analysis was completed, who performed the analysis ☐Sponsor ☐FDA

Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☐ Yes	☒ No	☒ Inadequate #'s	☐ Disease Absent
Safety	☐ Yes	☒ No	☒ Inadequate #'s	☐ Disease Absent

Was race-based analysis included in labeling?	
Yes	No
☐	☒
☐	☒

s a dosing modification based on race recommended in the label? ☐ Yes ☒ No

f the analysis was completed, who performed the analysis ☐Sponsor ☐FDA

e comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for
ı subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might
ered (including if labeling was modified).

ient:

Short bowel syndrome is classified as an orphan indication. The clinical program consisted primarily of a 3-arm, 41 patient, double-domized clinical trial. The data base recorded "Race" as Caucasian or "Non-Caucasian"

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 25, 2004

To: Lynda Sutton	**From: Tanya Clayton**
Company: Cato Research	
Fax number: 919-361-2290	**Fax number:** 301-443-9285
Phone number: 919-361-2286	**Phone number:** 301-827-4005

Subject: NDA 21-667

Total no. of pages including cover: 2

Comments:
Attached please find Labeling requests regarding NDA 21-667.

The requests is as follows:

1. Please provide a colored copy of the proposed carton/package labels for oral glutamine.

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/s/

Tanya Clayton
5/25/04 05:29:56 PM
CSO

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-667

Name of Drug: Glutamine Oral Powder

Sponsor: Nutritional Restart Pharmaceutical (Cato is the US agent)

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Electronic. This application was submitted in CTD format according to the 1999 guidance for submitting electronic NDAs. Module 1, Volume 1 is the only volume submitted in paper.

Submission Date: August 8, 2003

Receipt Date: August 11, 2003

Filing Date: October 10, 2003

User-fee Goal Date: June 11, 2004 (S)

Proposed Indication: Short Bowel Syndrome

Other Background Information: Serono, Inc. currently has an NDA in-process for the same indication. Action is due December 2003.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Module 1, Vol 1
2. Form FDA 356h (original signature)	X		Module 1, Vol 1
a. Establishment information		X	N/A
b. Reference to DMF(s) & Other			———

Applications	X		IND 48,750 (Serono)
3. User Fee FDA Form 3397 4. Patent information & certification	X		Module 1, Volume 1
5. Debarment certification (Note: Must have a definitive statement)	X		Module 1, Volume 1
6. Field Copy Certification	X		Module 1, Volume 1
7. Financial Disclosure	X		Module 1, Volume 1
8. Comprehensive Index	X		• **Each vol contains an overall TOC** • **Each study reports contains a TOC** • **Each file has a separate pagination**
9. Pagination	X		Each file has a separate pagination
10. Summary Volume	X		Module 2, Volumes 1-3
11. Review Volumes	X		Modules 3-5
12. Labeling (PI, container, & carton labels)			
a. unannotated PI	X		Module 1, Volume 1
b. annotated PI	X		Module 1, Volume 1
c. immediate container	X		Module 1, Volume 1
d. carton	X		Module 1, Volume 1
e. patient package insert (PPI)		X	N/A
f. foreign labeling (English translation)		X	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Electronic, Demographic Module 5, Volume 10
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Electronic, Individual Patient Listings Module 5, Volume 11

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Module 2, Volume 1 (Sect 2.51)
2. Foreign Marketing History			
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)		X	Chemistry section is in module 3
b. Nonclinical Pharmacology/Toxicology	X		Module 2, Volume 1 (Sect 2.4.2) (2.4.4)
c. Human Pharmacokinetic & Bioavailability	X		Module 2, Vol 3
d. Microbiology		X	N/A
e. Clinical Data & Results of Statistical Analysis	X		Module 2, Vol 3
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Module 2, Volume 1 (Sect 2.5.6)
5. Summary of Safety	X		Module 2, Volume 1 (Sect 2.55, 2.7.4)
6. Summary of Efficacy	X		Module 2, Volume 1 (2.54, 2.73)

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators		X	
2. Controlled Clinical Studies			
a. Table of all studies	X		Module 2, Volume 3 (Sect 2.7.6.1) Page 2
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)			Module 5, Volume 2
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Module 2, Volume 3 (Sect 2.7.6.3.1)
3. Integrated Summary of Efficacy (ISE)			
4. Integrated Summary of Safety (ISS)			
5. Drug Abuse & Overdosage Information	X		Module 2, Volume 1
6. Integrated Summary of Benefits & Risks of the Drug	X		Module 2, Volume 1
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	X		Module 2, Volume 1

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population			
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		X	N/A
a. Proposed unannotated labeling in MS WORD		X	
b. Stability data in SAS data set format (only if paper submission)		X	N/A
c. Efficacy data in SAS data set format (only if paper submission)		X	N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A
3. Exclusivity Statement (optional)			N/A

Y=Yes (Present), N=No (Absent)

[a]GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS (FEBRUARY 1987).

[b]GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS (FEBRUARY 1987).

[c]GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

e"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Additional Comments: Information request was sent October 10, 2003 for the labeling and Biopharmaceutic request.

Conclusions:

1. From an administrative prespective, this application is fileable.
2. A filing meeting is scheduled for September 26, 2003.

/S/

Tanya Clayton
Regulatory Project Manager

ADMINISTRATIVE REVIEW

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/s/

Tanya Clayton
5/18/04 11:01:06 AM
CSO

47 page(s) of revised draft labeling has been redacted from this portion of the review.

NDA 21-667

Foreign Labeling

This section is not applicable.

/S/ 5-18-04

Tanya Clayton
Regulatory Project Manager

NDA 21-667

Class Labeling

This section is not applicable.

S

Tanya Clayton
Regulatory Project Manager

5-18-04

25 page(s) of revised draft labeling has been redacted from this portion of the review.

A-5

NDA 21-667

DSI Report

This section is not applicable. The clinical study sites applicable to this NDA were also applicable to NDA 21-597, in which the sites were found acceptable July 2, 2003

/S/ 5.18.04

Tanya Clayton
Regulatory Project Manager

NDA 21-667

Postmarketing Commitments

There are no postmarketing commitments proposed for this cycle.

/S/ 5.18.04

Tanya Clayton
Regulatory Project Manager

NDA 21-667

Federal Register Notice

This section is not applicable.

/S/ 5.18.04

Tanya Clayton
Regulatory Project Manager

NDA 21-667

Public Communication

This section is not applicable.

5.18.04

Tanya Clayton
Regulatory Project Manager

NDA 21-667

Abuse/Liab Review

This section is not applicable.

/S/ 5.18.04

Tanya Clayton
Regulatory Project Manager

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 10, 2004

To: Lynda Sutton	**From: Tanya Clayton**
Company: Cato Research	
Fax number: 919-361-2290	**Fax number:** 301-443-9285
Phone number: 919-361-2286	**Phone number:** 301-827-4005

Subject: NDA 21-667

Total no. of pages including cover: 2

Comments:
Attached please find Chemistry and Labeling requests regarding NDA 21-667.

The requests are as follows:

1. Please provide a copy of the specifications for the Drug Product and Drug Substance to the NDA since they are included in the corresponding DMFs.

2. The Description section of the label should be revised in accordance to 21 CFR 201.57 (a).

3. The storage statement should be corrected to read:

   "Glutamine Powder for Oral Solution should be stored at 25°C (77°F) with excursions allowed to 15°-30°C (59-86°F). [See USP Controlled Room Temperature].

4. You should apply for a NDC number. (Refer to 21 CFR 207.35(6) (3)).

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/s/

Tanya Clayton
5/11/04 11:12:41 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-667

Cato Research
c/o Nutritional Restart Pharmaceutical, L.P.
Attention: Lynda Sutton, B.S.
Senior Vice President, Regulatory Affairs and Project Planning
200 Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oral Glutamine Packets™, (L-glutamine powder) 5g.

We also refer to your February 18, 2004 correspondence, received February 19, 2004 requesting a meeting to discuss the status of the Agency's review. We have considered your request and concluded that the meeting is unnecessary.

If you have any questions, call Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
2/26/04 12:20:08 PM

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: Feb 05, 2004	**DESIRED COMPLETION DATE:** April 16, 2004 **PDUFA DATE:** June 11, 2004	**ODS CONSULT #:** 04-0034

TO: Robert Justice, MD
Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Tanya Clayton
Project Manager
HFD-180

PRODUCT NAME: **Nutrestore™** (Glutamine Oral Powder) 5 gram packet **NDA #:** 21-667	**NDA HOLDER:** Nutritional Restart Pharmaceutical, L.P.

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Nutrestore™ from a safety perspective. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling 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 or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. [redacted]

/S/

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

/S/

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

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 20, 2004

NDA# 21-667

NAME OF DRUG: **Nutrestore**
(Glutamine Oral Powder) 5 gram packet

NDA HOLDER: Nutritional Restart Pharmaceutical, L.P.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastrointestinal Coagulation Drug Products (HFD-180), for assessment of the proprietary name, "Nutrestore", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Nutrestore contains L-glutamine which is indicated for use in short bowel syndrome as a co-therapy with rhGH (Serostim®) The recommended dose for oral glutamine powder is 30 grams daily, in divided doses of 5 grams six times per day. Nutrestore is to be used as a complement to four weeks of rhGH therapy and recommended for continued use subsequently (usual duration of treatment is sixteen weeks).

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Nutrestore 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[4] was also conducted. The Saegis Pharma-In-Use

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[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess2.uspto.gov/bin/gate.exe?f=tess&state=2fmprd.1.1
5. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

database[5] was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, for each proposed name, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Nutrestore. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and 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.

1. DDMAC does not recommend the use of the proprietary name, Nutrestore from a promotional perspective for the following reason "the name overstates the benefits of the drug because it suggests the drug will restore all nutrients, it is L-glutamine powder and is indicated for short bowel syndrome."

2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Nutrestore. The names are as follows: Metastron®, Natrecor®, Nitrostat®, and Nutracort®. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names for **Nutrestore** Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name, Available Strengths	Usual adult dose*	Other**
Nutrestore	Glutamine Oral Powder, 5 gram packets	5 grams/1 packet six times per day (30 grams daily)	
Metastron	Strontium Chloride (SR-89), Injectable/Injection 148 MBq, 4 mCi in 10 mL vial (10.9 to 22.6 mg/mL)	148 MBq, 4mCi by slow intravenous injection or 1.5 to 2.2 MBq per kilogram, 40 to 60 Ci per kilogram	LA
Natrecor	Nesiritide Solution for Intravenous Use 1.5 mg vial	2 mcg/kg per intravenous bolus followed by 0.01 mcg/kg/min	SA
Nitrostat	Nitroglycerin Sublingual Tablet 0.3 mg, 0.4 mg. 0.6 mg	1 sublingually or buccally, which may be repeated every 5 minutes, until relief or 3 tablets.	LA
Nutracort	Hydrocortisone Lotion 1% and 2.5% in 60 mL and 120 mL bottles	Use two to four times daily	SA/LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

5. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Nutrestore were discussed by the Expert Panel (EPD). No additional names of concern were identified in POCA that were not discussed in EPD.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology for Nutrestore:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Nutrestore with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of one-hundred and twenty-four health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and an outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Nutrestore (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: nutrestore 1 packet 6 x daily as dir #1 month supply	Nutrestore 1 packet six times daily as directed one month supply
Inpatient RX: Nutrestore 1 packet 6 time daily #180	

2. Results:

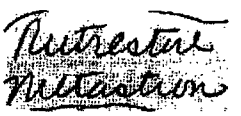
None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

1. Nutrestore

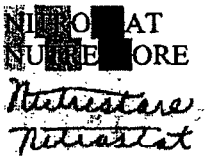
In reviewing the proprietary name Nutrestore, the primary concerns related to look-alike and/or sound-alike confusion with Metastron, Natrecor, Nitrostat and Nutracort. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Nutrestore.

a. Metastron looks similar to Nutrestore when scripted. Metastron contains Strontium-89 chloride indicated for the relief of bone pain in patient with skeletal metastases. It is dosed at 148 MBq, 4 mCi given per a slow intravenous injection with repeat doses occurring greater than 90 days subsequent. The drug is shipped and stored in a transportation shield with lead walls and maintained at room temperature. Upon comparisons of the names, the potential confusion is routed in specific similarities when written in cursive. This is especially true of the leading "Met" and "Nut" which can be difficult to differentiate when scripted. The following letters of "a" from Metastron and "re" from Nutrestore can also appear similar, since handwriting can narrow these central letters, henceforth losing definition. Although the phoneme confusion is not as significant, it is powered by the identical "st" appearing at a similar location in both names. This is complicated by the endings of "on" and "ore" that can also appear analogous due the same tendency to narrow the "ore" when scripted. This is also compounded by the tendency to taper the final letters of a name, which obscures the letters. See below.



However, there are no parallels upon product comparison. Metastron is a specialized radioactive intravenous medication administered to cancer patients as a one time dose for pain management. The medication has special handling requirements and expiration calculations (28 days after calibration). Despite the similarities when scripted, differences in strength, dosing regimen, indication, and route of administration minimize the risk of confusion between Metastron and Nutrestore.

b. Nitrostat looks similar to Nutrestore when scripted. Nitrostat contains nitroglycerin and is indicated for the acute relief or prophylaxis of angina pectoris. It is dosed at one tablet sublingually to be repeated every five minutes for a maximum of three tablets or until relief is obtained. Nitrostat is contained and dispensed in an amber glass vial. The potential name confusion is related to the strong similarities in the first seven letters when scripted, which is powered by the identical leading "N", central "TR" and ending "ST". The vowels ("i" followed by "o" versus "u" followed by "e") do not have the power to assist the reader in differentiating the names as they will be narrowed, obscured or blurred by the distinct consonants when scripted. This can be compounded by the fact that the differing endings of "at" of Nitrostat versus "ore" of Nutrestore may not carry the weight one would expect with a reader, since cursive handwritten orders tend to taper off possibly obscuring the identity of the ending letters.



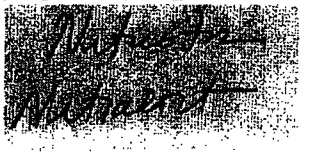
However, there are noteworthy differences in product characteristics. Although both are orally administered, the dosage forms differ with Nitrostat which is available as a tablet for sublingual use and Nutrestore will be available as a powder. In addition, strength or packaging do not overlap since Nitrostat is available in 0.3 mg, 0.4 mg or 0.6 mg strengths and packaged in bottles of 25 or 100 tablets versus Nutrestore that will be available as 5 gram packets and packaged in boxes of ninety. Dosing is also noticeably different and this difference is reinforced by health care providers' familiarity with the unique dosing of Nitrostat. Nitrostat's incremental dosing regimen for angina treatment is novel, widely prescribed and broadly understood in the health care area. Although the names can be viewed as similar upon scripting, the differences in available strengths, dosing regimens, dosage forms and product packaging may decrease name confusion and errors.

c. Natrecor sounds similar to Nutrestore. Natrecor contains human B-type natriuretic peptide indicated for use in patients with acutely decompensated congestive heart failure who have dyspnea at rest or minimal activity to reduce pulmonary capillary wedge pressure and improve dyspnea. The usual dosing is 2 micrograms per kilogram for a first bolus followed by a continuous infusion rate of 0.01 mcg/kg/min intravenously for less than 48 hours. Natrecor is available in a 1.5 mg vial to be reconstituted and added to an intravenous bag yielding a concentration of 6 mcg/mL. The basis for name confusion is the sharing of three key phonemes, the starting "N", middle "tre" and ending "or."

The leading vowels of "a" versus "u" do not have enough power for differentiation on a verbal order. Although, the "c" (spoken as a "k" sound) of Natrecor and "st" of Nutrestore should help differentiate the names, these distinctive sounds may be diluted by the strength of the "or" sound in regular speech. This is especially true as both names contain three syllables that are similar when spoken. However, significant differences in administration routes (intravenous versus oral), strengths (1.5 micrograms versus 5 grams), dosing regimen (continuous infusion for 48 hours versus daily dosing for up to three years), usual dose

(0.01 mcg per kilogram versus 5 grams) and prescriber population should diminish drug name confusion on verbal orders.

d. Nutracort looks and sounds similar to Nutrestore. Nutracort contains hydrocortisone at strength of 1% and 2.5%, which is indicated for relief of various topical inflammatory and pruritic manifestations and dosed at two to four times daily. Nutracort is available as a lotion in two and four ounce bottles. The primary look-alike and sound-alike confusion results from the identical leading letters of "Nutr." The names also share "or" in the third syllable.



Both names contains three syllables, which allows the final shared "or" (ȯr or ôr) to carry power in regular speech adding to name confusion. However, the force of the ending letter of "t" and phoneme of "st" of Nutrestore should help to differentiate the two names. Although practitioners will have the tendency to write both products using the directions of "as directed", there are also compelling dissimilarities such as strength (1% and 2.5% versus 5 grams), dosage form (lotion versus powder), route of administration (topical versus oral), dosing regimens (two to four times daily versus six times daily) and indication which should minimize the potential for confusion between these drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels of Nutrestore, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

DMETS recommends consulting CDER's Labeling and Nomenclature committee for the proper designation of the established name.

B. CONTAINER LABEL

1.

2.

3.

C. CARTON LABELING

1.

2.

1 page(s) of revised draft labeling has been redacted from this portion of the review.

A-6

V. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Nutrestore from a safety perspective. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling 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 and established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. [redacted]

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Kimberly Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: DMETS Prescription Study Results (Nutrestore)

Inpatient	Outpatient	Voice
Natrestine	Nutrentore	Nutrastore
Natrestere	Nutrestore	Nutrastore
Natrestere	nutrertore	Neutrostore
Natrestare	Nutrestore	Nutrastore
Nutrestere	Nutrestore	Nutrastore
Nutrastere	Nutrestore	Nutristore
Nutrastire	Nutrestore	Nutrastore
Natrestere	Nutrestore	Neutrastor
Natrestere	nutrestore	Nutrastore
Nutristore	Nutrestore	Neutrastore
Nutrestere	Nutrestore	NutraStore
Notresture	Nutrestore	Neutrastore
Natrestire	Nutrestore	Nutrastore
Natrestore	Nutrestore	neutrastore
Natrastere	Nutrestore	Neutrastor
Nutre Stere	Nutrestore	Neutrastore
Nutrastore	Nutrestore	Nutrastore
Natrestere	Nutrestore	Nutrastore
Natrestere	Nutrestore	Nutrastore
Natrestere	Nutrestore	Nutrastore
Natrestere	Nutrestore	Nutrastore
Nutrestere	nutrestore	Nutrastore
	Natrestere	

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/s/

Kimberly Culley
4/1/04 09:12:20 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
4/1/04 10:04:00 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/1/04 10:48:47 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
4/1/04 12:55:49 PM
DRUG SAFETY OFFICE REVIEWER

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	**REQUEST FOR CONSULTATION**

TO (Division/Office):	FROM:
Shannon Benedetto and Elaine Hu, HFD-42, Parklawn Building, Room 17B-17	Tanya Clayton (Consumer Safety Officer) GI and Coagulation Drug Products, HFD-180

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 4, 2004		21-667	New Drug Application	August 12, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Oral Glutamine	Standard	Misc. GI	April 16, 2004

NAME OF FIRM: Cato Research agent for Nutritional Restart Pharmaceutical, L.P.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☒ OTHER *(SPECIFY BELOW)*: Labeling Review
☐ MEETING PLANNED BY		

COMMENTS/SPECIAL INSTRUCTIONS:

This is a type 1New Drug Application that is being submitted for the treatment of short bowel syndrome. The PDUFA goal date is 06/11/04. Please note that this application was submitted electronically, consequently, it may be found on the EDR pathway – N 21667/08/08/03 (labeling) and N21667/29Jan04 (proposed tradename). Please let me know if you require additional information. Thank you in advance. Tanya Clayton – x774005.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Tanya Clayton
2/4/04 03:31:59 PM

18 page(s) of revised draft labeling has been redacted from this portion of the review.

A-8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-667

Cato Research
c/o Nutritional Restart Pharmaceutical, L.P.
Attention: Lynda Sutton, B.S.
Senior Vice President, Regulatory Affairs and Project Planning
200 Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

We received your December 8, 2003 correspondence on December 9, 2003 requesting a meeting to discuss the status of the Agency's review. We considered your request and concluded the meeting is premature.

If you disagree with our decision regarding your meeting request, you may discuss the matter with Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
1/7/04 04:43:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-667

Cato Research
c/o Nutritional Restart Pharmaceutical, L.P.
Attention: Lynda Sutton, B.S.
200 Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713-2280

Dear Ms. Sutton:

Please refer to your August 8, 2003 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oral Glutamine Packets™, (L-glutamine powder) 5g.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on October 10, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
10/20/03 09:30:00 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-667

Cato Research
Attention: Lynda Sutton, B.S.
200 Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Oral Glutamine

Review Priority Classification: Standard

Date of Application: August 8, 2003

Date of Receipt: August 11, 2003

Our Reference Number: NDA 21-667

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 10, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 11, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Courier/Overnight Mail/U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
10/15/03 02:18:34 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 10, 2003

To: Lynda Sutton	**From: Tanya Clayton**
Company: Cato Research	
Fax number: 919-361-2290	**Fax number:** 301-443-9285
Phone number: 919-361-2286	**Phone number:** 301-827-4005

Subject: NDA 21-667

Total no. of pages including cover: 2

Comments:
Attached please find requests for information regarding NDA 21-667.

The requests are as follows:

1. Please provide the proposed unannotated labeling in MS WORD by diskette (send directly to me).

2. Please confirm that you are not proposing a trade name.

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

/s/

Tanya Clayton
10/10/03 12:26:20 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 10, 2003

To: Lynda Sutton	**From: Tanya Clayton**
Company: Cato Research	
Fax number: 919-361-2290	**Fax number:** 301-443-9285
Phone number: 919-361-2286	**Phone number:** 301-827-4005

Subject: NDA 21-667

Total no. of pages including cover: 2

Comments:
Attached please find requests for information regarding NDA 21-667.

The requests are as follows:

1. According to the cited studies, the oral dose used covers up to 0.3g/kg (or 15g/50 kg) as a single dose. Please provide the PK information for oral formulation upon multiple dosing.

2. If available, please provide food effect studies. We recognize that food containing glutamine source can complicate the assay of blood glutamine, however, the label indicates that the dose should be taken with meals or snacks. In food effect studies are not available, please provide rationale for this.

3. Please provide studies in special populations (age, gender, race, renal impairment or hepatic impairment patients).

4. Please provide studies that examine the interaction between rhGh and glutamine.

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 26, 2003
Time: 2:00-3:30 p.m.
Location: Parklawn Building

Application: NDA 21-667

Type of Meeting: 45 Day Filing Meeting

Meeting Chair: Hugo Gallo Torres

Meeting Recorder: Tanya Clayton

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. Robert Justice; Division Director
Dr. Joyce Korvick; Deputy Division Director
Dr. Hugo Gallo-Torres; Medical GI Team Leader
Dr. Gary Della Zanna; Medical Reviewer
Dr. Liang; Acting Chemistry Team Leader
Dr. Maria Ysern; Chemistry Reviewer
Dr. Jasti Choudary; Pharmacology Team Leader
Dr. Ke Zhang; Pharmacology Reviewer

Division of Pharmaceutical Evaluation II (HFD-870)

Dr. Suresh Doddapaneni; Biopharmaceutic Team Leader
Dr. Sue Chih Lee; Biopharmaceutics Reviewer

Division of Biometrics III (HFD-720)

Dr. Tom Permutt; Statistical Team Leader
Dr. Dionne Price; Statistical Reviewer

Division of Scientific Investigations (HFD-45)

Dr. Khairy Malek; Medical Officer

Background: Nutritional Restart Pharmaceuticals (Cato, US agent) submitted NDA 21-667 on August 8, 2003 received August 12, 2003 for the proposed indication of short bowel syndrome. The filing date for this application is October 10, 2003.

Meeting Objective:

To determine the fileability of this application.

Discussion Points (bullet format):

I. Administrative

V Pharm/Tox

NO ISSUES/

Fileable

A. Filing Issues: None
B. Information Requests: None
C. Other Issues: None

Clinical

A. Filing Issues: None
B. Information Requests: None
C. Other Issues: None

(Include a summary of the clinical studies here)

II. Statistical

A. Filing Issues: None
B. Information Requests: None
C. Other Issues: None

III. Chemistry, Manufacturing and Controls

A. Filing Issues: None
B. Information Requests: None
C. Other Issues:
- Drug Substance, DMF is adequate
- Request for sites to be inspected
- Liang believes should be Type 1
- Have they requested user name?
- Do they want to propose a trade name?

IV. Biopharmaceutics

A. Filing Issues: None
B. Information Requests: Yes
C. Other Issues:

Conclusions:

1. It was agreed that the application **would** be filed.
2. An Information Request (IR) letter will be sent to the firm requesting the needed information.
3. It was agreed that we would commit to the **12 month** User Fee Goal Date of **June 11, 2004.** The following goal dates were set:
   - **June 11, 2004**= action goal date
   - May 7, 2004= completed action package to Dr. Justice
   - 2000 = all reviews completed (Division Goal Date) (allows __ weeks for CSO labeling review and action letter to be drafted and circulated to Team Leaders)

_____
Minutes Preparer:

_____
Chair Concurrence:

cc: Original NDA _____
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/A.Kacuba
HFD-180/L.Talarico
HFD-180/S.Aurecchia
HFD-180/H.Gallo-Torres/K.Robie-Suh
HFD-180/_____
HFD-180/L.Zhou
HFD-180/_____
HFD-180/J.Choudary
HFD-180/_____
HFD-870/D.Lee
HFD-870/_____
HFD-720/P.Flyer
HFD-720/_____
HFD-45/K.Malek

Drafted by: A.Kacuba/_____ __, 2000
Initialed by: K.Johnson/_____ __, 2000

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/s/

Tanya Clayton
11/24/03 02:54:07 PM

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Nutritional Restart Pharmaceutical, L.P.
Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

2. TELEPHONE NUMBER *(Include Area Code)*

(919) 361-2286

3. PRODUCT NAME

Oral Glutamine

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-667

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

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).

6. USER FEE I.D. 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)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	President, Nutritional Restart Pharmaceutical, L.P.	08/08/03

FORM FDA 3397 (4/01)

1.3.1.4 Field Copy Certification

I hereby certify, as required under 21 Code of Federal Regulation (CFR) 314.50(k)(3), that the field copy of Form FDA 356h and the Quality section (Module 3) are a true and exact copy as they are contained in the archival and review copies of this application.

In accordance with and as required under 21 CFR 314.4409(a)(4), the field copy is addressed to the following:

Food and Drug Administration
District Office
Center for Drug Evaluation and Research
60 Eighth St., N.E.
Atlanta, GA 30309
(404) 253-1163

Allen Cato M.D., Ph.D.
President
Nutrition Restart Pharmaceutical, L.P.

Allen Cato
Signature

8-7-03
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Allen Cato, M.D., Ph.D.	President
FIRM / ORGANIZATION: Nutritional Restart Pharmaceutical, L.P.	
SIGNATURE: Allen Cato	DATE: 7/24/03

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (2/03)

Created by: FSC Media Arts Branch (301) 443-1090 EF

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

March 6, 1995

Cato Research
Attention: Susan Watts, Ph.D.
200 Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

Dear Dr. Watts:

Reference is made to your orphan drug application of January 19, 1994 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of glutamine as an orphan drug (application #94-857). We also refer to your amendment dated January 16, 1995.

We have completed the review of this application, as amended, and have determined that glutamine qualifies for orphan designation for use with human growth hormone in the treatment of short bowel syndrome (nutrient malabsorption from the gastrointestinal tract resulting from an inadequate absorptive surface). Please note that it is glutamine and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if glutamine were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of glutamine as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. Wayne Turner at (301) 443-4718.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Director

cc:
HFD-85/M.A.Holovac
HFD-180
HF-35/OP File #94-857
HF-35/W.Turner
HF-35/chron
HF-35/P.Vaccari 3/6/95 dsg.857

3/6/95

NDA ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-667		
Drug: NutreStore™ (Glutamine Powder for Oral Solution)	Applicant: Nutritional Restart Pharmaceutical, L.P. c/o Cato Research	
RPM: Tanya Clayton	HFD-180	Phone 301-827-4005
Application Type: ( ) 505(b)(1) (X) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): 21-597/Serostim	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	1, NME
• Other (e.g., orphan, OTC)	Orphan, March 6, 1995
❖ User Fee Goal Date	June 11, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	(X) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III (X) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	(X) Verified

Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes (X) No
❖ Administrative Reviews (Project Manager, signed May 18, 2004; ADRA , signed ❖ June 2, 2004)	X
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X (labeling meeting to be held May 21, 2004)
• Most recent applicant-proposed labeling *(dated May, 2003)*	X
• Original applicant-proposed labeling *(dated May, 2003)*	X
• Labeling reviews (Office of Drug Safety trade name review) • *ODS DMETS- April 1, 2004* • *ODS DDMAC – March 23, 2004 and April 1, 2004*	X (DMETS tradename) X(DDMAC)
• Other relevant labeling (e.g., most recent 3 in class)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed (August 8, 2003)	X
• Reviews	X (ODS DMETS tradename)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• Filing meeting (September 26, 2003)	X

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)-Tentative Final Monograph	N/A
Summary Application Review	
❖ Summary Review (e.g., Office Director, Division Director, Medical Team Leader) ❖ *(June 3, 2004)*	X
Clinical Information	
❖ Clinical review (May 25, 2004)	X
❖ Microbiology (efficacy) review	N/A
❖ Safety Update review (included in clinical review)	X
❖ Pediatric Page (separate page for each indication addressing status of all age groups) – June 9, 2004	X
❖ Demographic Worksheet *(NME approvals only)*	X
❖ Statistical review (May 16, 2004)	X
❖ Biopharmaceutical (May 10, 2004)	X
❖ Controlled Substance Staff review and recommendation for scheduling	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC reviews (April 29, 2004, June 4, 2004)	X
❖ Environmental Assessment	
• Categorical Exclusion	X
• Review & FONSI	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility	N/A
❖ Facilities inspection (provide EER report) (March 18, 2004)	X
❖ Methods validation	Post approval, mentioned in AP Letter
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review, including referenced IND reviews (May 7, 2004)	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review of carcinogenicity studies	N/A
❖ CAC/ECAC report	N/A