CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-712

Name: Lactulose for Oral Solution, 10 g and 20 g single-dose packets

Sponsor: Inalco, S.P.A

Approval Date: December 10, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-712

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-712

APPROVAL LETTER

ANDA 74-712

DEC 10 1997

L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for: Inalco, S.p.A.
315 East 68th Street
New York, NY 10021

Dear Sir:

This is in reference to your abbreviated new drug application dated July 14, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lactulose for Oral Solution, 10 g and 20 g single-dose packets.

Reference is also made to your amendments dated July 30, September 4, and December 3, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug can be expected to have the same therapeutic effect as that of the reference listed drug product upon which the agency relied as the basis of safety and effectiveness.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gordon R. Johnston for

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

12/10/97

cc: ANDA 74-712
Division File
Field Copy
HFD-610/JPhillips
HFD-600/Reading File
HFD-92
HFD-330
HFD-210/BPoole

Endorsements:

HFD-645/KBernard/9/5/97/ K Bernard 9/11/97
HFD-617/KSherrod/9/8/97/ K Sherrod 9/11/97
HFD-613/JJohnson J Johnson 9/11/97 acting per 9/12/97
HFD-645/BArnwine/ALangowski/9/10/97/ A Langowski for B. Arnwine 9/11/97
x:\new\firmsam\inalco\ltrs&rev\74712dl.apf
F/T by VLJ/9/11/97

Approvable

12/3/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-712

LABELING

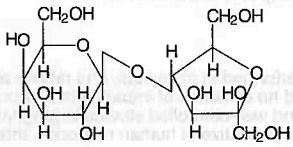
LACTULOSE FOR ORAL SOLUTION

DESCRIPTION

Lactulose is a synthetic disaccharide in the form of crystals for reconstitution prior to use for oral administration. Each 10 g of lactulose contains less than 0.3 g galactose and lactose as a total sum. The pH range is 3.0 to 7.0.

Lactulose is a colonic acidifier which promotes laxation.

The chemical name for lactulose is 4-O-β-D-Galactopyranosyl-D-fructofuranose. It has the following structural formula:



The molecular formula is $C_{12}H_{22}O_{11}$. The molecular weight is 342.30. It is freely soluble in water.

CLINICAL PHARMACOLOGY

Lactulose is poorly absorbed from the gastrointestinal tract and no enzyme capable of hydrolysis of this disaccharide is present in human gastrointestinal tissue. As a result, oral doses of lactulose reach the colon virtually unchanged. In the colon, lactulose is broken down primarily to lactic acid, and also to small amounts of formic and acetic acids, by the action of colonic bacteria, which results in an increase in osmotic pressure and slight acidification of the colonic contents. This in turn causes an increase in stool water content and softens the stool.

Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce the desired bowel movement.

Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

INDICATIONS AND USAGE

Lactulose for Oral Solution is indicated for the treatment of constipation. In patients with a history of chronic constipation, lactulose therapy increases the number of bowel movements per day and the number of days on which bowel movements occur.

CONTRAINDICATIONS

Since Lactulose for Oral Solution contains galactose (less than 0.3 g/10 g as a total sum with lactose), it is contraindicated in patients who require a low galactose diet.

WARNINGS

A theoretical hazard may exist for patients being treated with lactulose who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H_2 gas in significant concentration in the presence of an electrical spark may result in an explosive reaction. Although this complication has not been reported with lactulose, patients on lactulose therapy undergoing such procedures should have a thorough bowel cleansing with a non-fermentable solution. Insufflation of CO_2 as an additional safeguard may be pursued but is considered to be a redundant measure.

PRECAUTIONS

General

Since Lactulose for Oral Solution contains galactose and lactose (less than 0.3 g/10 g as a total sum), it should be used with caution in diabetics.

Information for Patients

In the event that an unusual diarrheal condition occurs, contact your physician.

Laboratory Tests

Elderly, debilitated patients who receive lactulose for more than six months should have serum electrolytes (potassium, chloride, carbon dioxide) measured periodically.

Drug Interactions

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose.

Carcinogenesis, Mutagenesis, Impairment of Fertility
There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility.

There are no known animal data on long-term potential for mutagenicity.

Administration of lactulose syrup in the diet of mice for 18 months in concentrations of 3 and 10 percent (v/w) did not produce any evidence of carcinogenicity.

In studies in mice, rats, and rabbits, doses of lactulose syrup up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Pregnancy
Teratogenic Effects
Pregnancy Category B
Reproduction studies have been performed in mice, rats, and rabbits at doses up to 3 or 6 times the usual human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to lactulose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Precise frequency data are not available.

Initial dosing may product flatulence and intestinal cramps, which are usually transient. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia.

Nausea and vomiting have been reported.

OVERDOSAGE
Signs and Symptoms
There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated.

Oral LD_{50}
The acute oral LD_{50} of the drug is 48.8 mL/kg in mice and greater than 30 mL/kg in rats.

Dialysis
Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

DOSAGE AND ADMINISTRATION
The usual adult dosage is 10 g to 20 g of lactulose daily. The dose may be increased to 40 g daily if necessary. Twenty-four to 48 hours may be required to produce a normal bowel movement.

DIRECTIONS FOR PREPARATION
Dissolve contents of packet in half a glass (4 ounces) of water.

When Lactulose for Oral Solution is dissolved in water, the resulting solution may be colorless to a slightly pale yellow color.

HOW SUPPLIED
Lactulose for Oral Solution is available in 10 g and 20 g single dose packets in cartons of 50.

Store at room temperature, 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

NDC: 0472-1356-10
0472-1356-20

Rev: 0

Distributed by
Alpharma USPD Inc.
Baltimore, MD 21244

Manufactured by
Inalco S.p.A.
Milan, Italy

NDC 0472-1356-10

LACTULOSE FOR ORAL SOLUTION

ALPHARMA™

10 Grams

DEC 1

CAUTION: Federal law prohibits dispensing without prescription.

Single Dose Packet

Distributed by **Alpharma USPD Inc.,** Baltimore, MD 21244

CONTENT: Each packet contains 10 grams lactulose (and less than 0.3 g galactose and lactose as a total sum).

USUAL ADULT DOSAGE: 10 to 20 grams daily. See accompanying package insert.

DIRECTIONS FOR PREPARATION: Dissolve contents of packet in half a glass (4 ounces) of water.

Store at room temperature, 15°-30°C (59°-86°F).

Manufactured by
Inalco S.p.A
Milan, Italy

Lot No.:

Expiration date:

APPRO...D

NDC 0472-1356-20

LACTULOSE FOR ORAL SOLUTION

ALPHARMA™

20 Grams

CAUTION: Federal law prohibits dispensing without prescription.

Single Dose Packet

Distributed by **Alpharma USPD Inc.,** Baltimore, MD 21244

CONTENT: Each packet contains 20 grams lactulose (and less than 0.6 g galactose and lactose as a total sum).

USUAL ADULT DOSAGE: 10 to 20 grams daily. See accompanying package insert.

DIRECTIONS FOR PREPARATION: Dissolve contents of packet in half a glass (4 ounces) of water.

Store at room temperature, 15°-30°C (59°-86°F).

Manufactured by
Inalco S.p.A
Milan, Italy

DEC 10 1997

APPROVED

Lot No.:

Expiration date:

10 Grams

LACTULOSE FOR
ORAL SOLUTION

NDC 0472-1356-10

NDC 0472-1356-10

LACTULOSE FOR ORAL SOLUTION

ALPHARMA™

10 Grams

CAUTION: Federal law prohibits dispensing without prescription.

50 Single Dose Packets

Distributed by **Alpharma USPD Inc.,** Baltimore, MD 21244

Each packet contains 10 grams lactulose and less than 0.3 g galactose and lactose as a total sum.

This unit-dose packet is not child resistant.

INDICATIONS: For the treatment of constipation. See accompanying package insert.

USUAL ADULT DOSAGE: 10 to 20 grams daily. See accompanying package insert.

Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 – 48 hours may be required to produce a normal bowel movement.

DIRECTIONS FOR PREPARATION: Dissolve contents of packet in half a glass (4 ounces) of water.

Store at room temperature, 15°-30°C (59°-86°F).

Manufactured by
Inalco S.p.A.
Milan, Italy

Lot No.:

Expiration date:

NDC 0472-1356-10

LACTULOSE FOR ORAL SOLUTION

ALPHARMA™

10 Grams

APPROVED
DEC 10 1997

CAUTION: Federal law prohibits dispensing without prescription.

50 Single Dose Packets

Distributed by **Alpharma USPD Inc.**, Baltimore, MD 21244

NDC 0472-1356-20

LACTULOSE FOR ORAL SOLUTION

ALPHARMA™

20 Grams

APPROVED

DEC 10 1997

CAUTION: Federal law prohibits dispensing without prescription.

50 Single Dose Packets

Distributed by **Alpharma USPD Inc.**, Baltimore, MD 21244

NDC 0472-1356-20

LACTULOSE FOR ORAL SOLUTION

ALPHARMA™

20 Grams

Each packet contains 20 grams lactulose and less than 0.6 g galactose and lactose as a total sum.

This unit-dose packet is not child resistant.

INDICATIONS: For the treatment of constipation. See accompanying package insert.

USUAL ADULT DOSAGE: 10 to 20 grams daily. See accompanying package insert.

Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 – 48 hours may be required to produce a normal bowel movement.

DIRECTIONS FOR PREPARATION: Dissolve contents of packet in half a glass (4 ounces) of water.

Store at room temperature, 15°-30°C (59°-86°F).

Manufactured by
Inalco S.p.A.
Milan, Italy

Lot No.:

Expiration date:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-712

LABELING REVIEWS

FIRST GENERIC
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: March 19, 1996

ANDA Number: **74-712** Review Cycle: **1** (Draft labels and labeling)

Dates of Submission: July 14, 1995 (Original Submission - RTF)
September 14, 1995 (AC - RTF)
December 1, 1995 (AC - Accepted for Filing)

Applicant's Name [as seen on 356(h)]: **Inalco SpA**

Manufacturer's Name (If different than applicant): Same

Proprietary Name: None

Established Name: **Lactulose for Oral Solution, 10 g unit dose packets**

1° Reviewer: D.Konigstein

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

1. GENERAL COMMENTS

   a. Please revise the established name on your labels and labeling to read "Lactulose for Oral Solution" rather than "Lactulose (b) (4) ".

   b. Provide specific instructions on the preparation of a dose. Please address these issues:

   - Should the patient or provider be further cautioned against consuming the dry form, rather than just "... should be dissolved in water immediately prior to administration"?
   - What volume of fluid is desirable to mix a dose with?
   - Can the product be mixed in fluids other than water?
   - What does one do when a larger dose is prepared and multiple packets are used?
   - Please note that the usual dosage is 10 to 20 grams. How does a patient or provider prepare an intermediate dose (i.e, 15 g)?
   - Please state if the resulting solution has a color or is it colorless?

   Revise your labels and labeling accordingly.

c. You are required to obtain an NDC number for your product and you are encouraged to include it on your labels and labeling. See 21 CFR 207.35 for further guidance.

2. CONTAINER - 10 g packet

a. Relocate "10 grams" to follow the established name and use "Single Dose Packet" rather than "(b) (4)".

b. Revise the "Contents" statement to read "Each packet contains 10 grams lactulose (and less ..."

c. Delete the statement "(b) (4) see accompanying package insert." and revise the "Usual Adult Dose" statement to read:

> Usual Adult Dosage: (b) (4) daily. See accompanying package insert.

d. If room permits, include the storage recommendation statement.

e. See GENERAL COMMENTS above.

3. CARTON

a. See GENERAL COMMENTS above.

b. Relocate "10 grams" to follow the established name and use (b) (4) Single Dose Packets" rather than "(b) (4)".

c. Revise the "Each 10 grams" statement to read:

> Each packet contains 10 grams lactulose and less than 0.3 g of galactose and lactose as a total sum.

d. Include the storage recommendation statement.

e. Revise the "Indications and Usage" section to read as follows:

> Indications: For the treatment of constipation. See accompanying package insert.

f. Delete the statement "(b) (4) see accompanying package insert." and revise the "Usual Adult Dose" statement to read:

Usual Adult Dosage: (b) (4) daily. See accompanying package insert.

Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce a normal bowel movement.

4. INSERT

a. DESCRIPTION

i. First paragraph, third sentence - Include the pH range of the resultant solution when mixed according to directions.

ii. 4-*O*-B-D-Galactopyranosyl ... [italic "*O*" and capital "G"]

iii. Include the molecular formula.

b. CLINICAL PHARMACOLOGY

First paragraph, third sentence - ... amounts of formic and acetic acids, ... [delete '(b) (4)'].

c. INDICATIONS AND USAGE

Revise the first paragraph to read:

Lactulose for Oral Solution is indicated for the treatment of constipation. In patients ...

d. CONTRAINDICATIONS

Revise to read:

Since Lactulose for Oral Solution contains galactose ...

e. PRECAUTIONS

i. General - See comment d, CONTRAINDICATIONS.

ii. Pediatric Use - Use "pediatric patients" rather than "(b) (4)".

f. OVERDOSAGE

Signs and Symptoms, second sentence - "symptoms" [plural].

g. DOSAGE AND ADMINISTRATION

i. First paragraph - Revise to read:

> The usual adult dosage is 10 g to 20 g ((b) (4)) of lactulose daily. The dose may be increased to 40 g ((b) (4) daily if necessary. Twenty-four ...

ii. See comment b under GENERAL COMMENTS.

h. HOW SUPPLIED

i. See comment c under GENERAL COMMENTS.

ii. Delete reference to the "20 g (b) (4) pouch" and revise to include the established name, dosage form and container size. For example:

> Lactulose for Oral Solution is available in 10 g single dose packets in cartons of (b) (4)

iii. Revise the storage recommendation to read:

> Store at room temperature 15°-30°C (59°-86°F).

iv. We encourage the inclusion of the "Caution: Federal law ..." statement.

i. Per 21 CFR 201.56(e), place the revision date prominently immediately following the last section of the insert.

Please revise your container label and carton and insert labeling, as instructed above, and submit draft labels and labeling.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name - SEE FTR	**Yes**	**No**	**N.A.**
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?			X
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME - None			
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?			
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths? SEE FTR		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring:			X
Inactive Ingredients: "None"			X
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			X
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			X
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: See FTR			X
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?	X		
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: See FTR			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: None			

FOR THE RECORD:

1. BASIS OF REVIEW: The review was based on Chronulac®; Merrell Dow; Revised April 1985. (No approval date is stamped on it, but it is used as the model in the folder. SLR-012; approvable on 8-24-84, is probably an earlier version of this 4/85 model and no notation is present to

list any acknowledged and retained status in the MIS. The MIS system's last approved labeling for NDA 17-884 was SLR-010 on 10-22-81.)

2. PETITION PRODUCT - This company filed a suitability petition for this dosage form. However, they only were granted for a 10 g product. They filed the ANDA for a 10 g and a 20 g product. We refused to file it until they deleted reference to the 20 g. However, they replied that they then submitted a petition for the 20 g on 8-21-95 and will amend once they got approval. The first petition was turned around in less than 3 months. 7 months have elapsed on the 20 g petition... If they heard back, they haven't amended. The firm withdrew the 20 g product on 12-1-95. The 20 g labels were not reviewed and the firm is being asked to delete reference to the 20 g product in the HOW SUPPLIED section.

When they file the 20 g, the comment to differentiate their products will be made.
Noted that the MIS system hasn't been modified to delete 20 g from the name of the product.

THIS IS A FIRST GENERIC.

3. ESTABLISHED NAME - The firm uses "Lactulose (b) (4) '. Outgoing correspondence from OGD uses "Lactulose for Oral Solution". The "petitions approved" listing, in Orange Book, calls this product "Lactulose Crystal; Oral". The firm is asked to revise their established name to be "Lactulose (b) (4) for Oral Solution".

4. This is not a USP product.

5. INACTIVE INGREDIENTS - There aren't any per the firm's components and composition statement on p. 46.

6. PATENTS/EXCLUSIVITIES - None

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
USP for Oral Solution: Preserve in tight containers, preferably at a temperature between 2° and 30°C. Avoid subfreezing temperatures.
Oral Solution NDA: Store at room temperature, below 86°F (30°C). Do not freeze.
ANDA:Store at room temperature 15°-30°C (59°-86°F)

8. DISPENSING STATEMENTS COMPARISON
NDA: Dispense in tight, light-resistant container with child-resistant closure.
ANDA: None. However, the packets are sealed and are thought to be tight, light-resistant.

9. BIOEQUIVALENCE - Pending. Waiver requested. Products are AA rated in O Book.

10. PACKAGING CONFIGURATIONS
NDA: 240 mL, 960 mL, and 30 mL unit-dose cups in cartons of 100.
ANDA: 10 g single dose packets in cartons of (b) (4) Never before on the market.

11. I borrowed wording from cholestyramine packets. I request the firm use "single dose packets" rather than "(b) (4)". the patient will get the whole box. Does the average person know what "(b) (4)' means?
Also, after the firm proposes preparation information, I will consider changing the heading "Directions" to "Preparation". Numerous issues for firm to address regarding preparation asked in General Comments. Labeling from the cholestyramine product seems good to use if their future proposed wording is inadequate:

> [Lactulose for Oral Solution] should not be taken in its dry form. Always mix [Lactulose for Oral Solution] with water before ingesting. See preparation instructions.

12. There is a For The Record in the model folder stating that OGD will require the indication on the container/carton of lactulose products.

13. NDC NUMBERS - The firm stated in their side-by-side comparison for the container labels (in 9-14-95 amendment): "Proposed product has no NDC number. NDC number has not been selected or assigned." And in the insert: "Delete references to NDC numbers. NDC numbers not applicable to generic product." I don't know if they are referring to the fact that the RLD's NDC numbers are obviously not to be used on their product or aren't applicable, period. Anyway, no NDC numbers are present and a comment was made obtain.

D Konigstein 3.21-96

David Konigstein, Date
Primary Reviewer

John Grace 3-21-96

Acting John Grace Date
Acting Team Leader,
Labeling Review Branch

cc: ANDA 74-712
Dup
Division File
see x:\new\firmsam\inalco\ltrs&rev\74712na1.l

Phillips 3/25/96

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-712** Date of Submission: August 5, 1996

Applicant's Name: **Inalco SpA**

Established Name:
Lactulose for Oral Solution, 10 g and 20 g single dose packets

Labeling Deficiencies:

1. GENERAL COMMENT

   We remind you that when draft labeling is submitted, four copies of each item are required.

2. CONTAINER - 10 g and 20 g Single Dose Packets

   a. We encourage you to differentiate your product strengths by the use of contrasting colors, boxing, or some other means.

   b. Usual Adult Dosage - Revise to read:

      10 to 20 grams daily. See accompanying package insert.

   c. Revise "Directions" to read "Directions for Preparation" and revise to read:

      Dissolve contents of packet in half a glass (4 ounces) of water.

3. CARTON - (b)(4) (10 g and 20 g)

   a. See comments under Container.

   b. Is the unit-dose package child-resistant? If it is not, include the statement "This unit-dose package is not child-resistant."

   c. 10 g - Store ... 15°-30°C (59°-86°F). [°C first]

4. INSERT

   a. DESCRIPTION

      Paragraph 1

i. Sentence 2 - Delete the comma after "galactose."

ii. Delete the last two sentences "The pH ... (b) (4) [redacted]"

b. PRECAUTIONS

General, paragraph 1 - Revise to read "... than 0.3 g/10 g as a total sum), it ..."

c. DOSAGE AND ADMINISTRATION

i. Paragraph 1

Delete "(b) (4) [redacted] in the first and second sentences, respectively.

ii. Insert the subsection heading "Directions for Preparation" after the first paragraph.

iii. Paragraph 2 - Revise to read:

Dissolve contents of packet in half a glass (4 ounces) of water.

iv. We acknowledge your proposal regarding intermediate dosages, however, upon further review, we find your original proposed draft acceptable without this information. Please delete paragraph 3.

v. Regarding the color of the resultant solution: You indicate it "may" have a slightly pale yellow color. Could it be colorless? If not, it would be appropriate to indicate that it "has" a slightly pale yellow color". If so, "... may be colorless to a slightly pale yellow color" would be more descriptive. Please comment and/or revise.

d. HOW SUPPLIED

We encourage the inclusion of the "Caution: Federal law ..." statement in this section.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container (packet) labels and carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

_____

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?	X		
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. PETITION PRODUCT - At the time of the first review, only the 10 g suitability petition for this dosage form was approved. The 20 g petition was approved on 4-19-96. Revisions to the insert were requested based on that. However, now the 20 g info is back in and reviewed accordingly. So, thus could be considered a first generic.

2. MODEL LABELING - The review was based on Chronulac®; Merrell Dow; Revised April 1985. (No approval date is stamped on it, but it is used as the model in the folder. SLR-012; approvable on 8-24-84, is probably an earlier version of this 4/85 model and no notation is present to list any acknowledged and retained status in the MIS. The MIS system's last approved labeling for NDA 17-884 was SLR-010 on 10-22-81.) Also available was a side-by-side from the RLD's Y-16 dated 8-16-91. Essentially the same except for the inclusion of the pH range.

3. This is not a USP product.

4. INACTIVE INGREDIENTS - There aren't any per the firm's components and composition statement on p. 46.

5. PATENTS/EXCLUSIVITIES - None

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   USP for Oral Solution: Preserve in tight containers, preferably at a temperature between 2° and 30°C. Avoid subfreezing temperatures.
   Oral Solution NDA: Store at room temperature, below 86°F (30°C). Do not freeze.
   ANDA: Store at room temperature 15°-30°C (59°-86°F)

7. DISPENSING STATEMENTS COMPARISON - CHILD RESISTANCE
   NDA: Dispense in tight, light-resistant container with child-resistant closure.
   ANDA: None. However, the packets are sealed and are thought to be tight, light-resistant. The comment was made in this review to add a statement that it is not child-resistant. The usual comment was modified to omit info about dispensing in a child resistant container since it is not plausible.

8. BIOEQUIVALENCE - Waiver granted 3-27-96. Bio review completed about the same time as first labeling review and reviewer advised chemistry and labeling that no procedures for reconstitution are noted in the firm's labeling. Procedures are being addressed.

9. PACKAGING CONFIGURATIONS
   NDA: 240 mL, 960 mL, and 30 mL unit-dose cups; 100s.
   ANDA: 10 g and 20 g single dose packets in cartons of (b) (4)
   Never before on the market.

10. ESTABLISHED NAME - The firm has revised to "Lactulose for Oral Solution". The "petitions approved" listing, in Orange Book, calls this product "Lactulose Crystal; Oral".

11. There is a For The Record in the model folder stating that OGD will require the indication on the container/carton of lactulose products.

12. INTERMEDIATE DOSING - We first asked the firm to address the preparation of an intermediate dose based on the range stated in the D & A section. The firm came back and proposed (b) (4)

At first, I had prepared a Note to the Chemist to confirm this and thought a dosing table might be appropriate for the D & A section. But it was then pointed out to me by other reviewers that, within the meaning of a Single Dose Packet, is that it could not be split. It is a "SINGLE DOSE" and counter to measuring! It would be too confusing for consumers. Then what about stability of open packets? And so on.

All other lactulose products are solutions with fixed concentrations and an intermediate dose is obtainable easily. As well, to have labeling the same as the innovator - this would fall out of line. It was decided that this issue will not be pursued. Dosing would have to be in even quantities, which is probably what takes place out there for the most part. By no means is an accurate dose necessary or is this a narrow therapeutic range drug. If an intermediate dose is necessary, we will have to leave it up to prescribers to choose the right product.

Date of Review: 12/9/96 (Revised 12-19-96) **Date of Submission: 8/5/96**

Primary Reviewer: DKonigstein **Date:** 12-19-96

Secondary Reviewer: A. Vezza **Date:** 12-20-96

Team Leader: Aubrey Vezza (for J. Grace) Acting Team Leader **Date:** 12-20-96

cc: ANDA 74-712
DUP/DIVISION FILE
HFD-613/DKonigstein/AVezza/JGrace (no cc)
dk/12/19/96/x:\new\firmsam\inalco\ltrs&rev\74712na2.l

REVIEW

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-712** Date of Submission: **May 23, 1997**

Applicant's Name: **Inalco SpA**

Established Name: **Lactulose for Oral Solution, 10 g and 20 g single dose packets**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes (9-blue) (3-red)

Container Labels: 10 g and 20 g Single Dose Packets

Satisfactorily submitted May 23, 1997.

Carton Labeling: (b) (4) (10 g and 20 g)

Satisfactorily submitted May 23, 1997.

Professional Package Insert Labeling:

Satisfactorily submitted May 23, 1997.

Revisions needed post-approval: **CARTON** (1) This unit-dose package ... (rather than "packet") (2) ... 24 to 48 hours ... (rather than "24-48 hours" **INSERT** - Delete the last sentence of the first paragraph of the DESCRIPTION section (The pH ...).

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes

What is the RLD on the 356(h) form: Chronulac® (Lactulose sol.)

NDA Number: 17-884

NDA Drug Name: Chronulac® (Lactulose solution)

NDA Firm: Marion Merrell Dow

Date of Approval of NDA Insert and supplement #: 10/22/81 (S-010)
The model used for this review is Rev. April 1985 - see FTR

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: **RLD container labels in file folder - see FTR**

Basis of Approval for the Carton Labeling: **RLD container labels in file folder - see FTR**

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?	X		
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD: (Most of comments taken from previous review.)

1. PETITION PRODUCT - At the time of the first review, only the 10 g suitability petition for this dosage form was approved. The 20 g petition was approved on 4-19-96. Revisions to the insert were requested based on that. However, now the 20 g info is back in and reviewed accordingly. So, thus could be considered a first generic.

2. MODEL LABELING - The review was based on Chronulac®; Merrell Dow; Revised April 1985. (No approval date is stamped on it, but it is used as the model in the folder. SLR-012; approvable on 8-24-84, is probably an earlier version of this 4/85 model and no notation is present to list any acknowledged and retained status in the MIS. The MIS system's last approved labeling for NDA 17-884 was SLR-010 on 10-22-81.) Also available was a side-by-side from the RLD's Y-16 dated 8-16-91. Essentially the same except for the inclusion of the pH range.

3. This is not a USP product.

4. INACTIVE INGREDIENTS - There aren't any per the firm's components and composition statement on p. 46 vol 1.1.

5. PATENTS/EXCLUSIVITIES - None

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
USP for Oral Solution: Preserve in tight containers, preferably at a temperature between 2° and 30°C. Avoid subfreezing temperatures.
Oral Solution NDA: Store at room temperature, below 86°F (30°C). Do not freeze.
ANDA: Store at room temperature 15°-30°C (59°-86°F)

7. DISPENSING STATEMENTS COMPARISON - CHILD RESISTANCE
NDA: Dispense in tight, light-resistant container with child-resistant closure.
ANDA: None. However, the packets are sealed and are thought to be tight, light-resistant. The firm was asked to label the container "This unit-dose package is not child resistant." Firm put "packet" instead of "package". This can be a future revision. The usual comment was modified to omit info about dispensing in a child resistant container since it is not plausible.

8. BIOEQUIVALENCE - Waiver granted 3-27-96. Bio review completed about the same time as first labeling review.

9. PACKAGING CONFIGURATIONS
NDA: 240 mL, 960 mL, and 30 mL unit-dose cups; 100s.
ANDA: 10 g and 20 g single dose packets in cartons of (b) (4)
Never before on the market.

10. ESTABLISHED NAME - The firm has revised to "Lactulose for Oral Solution". The "petitions approved" listing, in Orange Book, calls this product "Lactulose Crystal; Oral".

11. There is a For The Record in the model folder stating that OGD will require the indication on the container/carton of lactulose products.

12. INTERMEDIATE DOSING - We first asked the firm to address the preparation of an intermediate dose based on the range stated in the D & A section. The firm came back and proposed (b) (4)

At first, I had prepared a Note to the Chemist to confirm this and thought a dosing table might be appropriate for the D & A section. But it was then pointed out to me by other reviewers that, within the meaning of a Single Dose Packet, is that it could not be split. It is a "SINGLE DOSE" and counter to measuring! It would be too confusing for consumers. Then what about stability of open packets? And so on.

All other lactulose products are solutions with fixed concentrations and an intermediate dose is obtainable easily. As well, to have labeling the same as the innovator - this would fall out of line. It was decided that this issue will not be pursued. Dosing would have to be in even quantities, which is probably what takes place out there for the most part. By no means is an accurate dose necessary or is this a narrow therapeutic range drug. If an intermediate dose is necessary, we will have to leave it up to prescribers to choose the right product.

13. The firm was asked in the previous review to delete the last two sentences of the first paragraph of the DESCRIPTION section. They only deleted the last one. This can be post-approval. The sentence is "The pH range is 3.0 to 7.0". This sentence is in the innovator labeling - in Y-16 dated 8-16-91 and **not** in the last approved labeling for the product. Since the ANDA drug product is crystals and the latest approved RLD does not have this statement it was felt that it could be deleted.

Date of Review: May 30, 1997 **Date of Submission: 5/23/97**

Primary Reviewer: Adolph Vezza **Date:** 6-2-97

Team Leader: John Grace **Date:** 6/2/97

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cc:

ANDA: 74-712
DUP/DIVISION FILE
HFD-613/AVezza/JGrace (no cc)
njg/6/2/97|X:\NEW\FIRMSAM\INALCO\LTRS&REV\74712.APL
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-712

CHEMISTRY REVIEWS

1. CHEMIST'S REVIEW NO.1

2. ANDA # 74-712

3. NAME AND ADDRESS OF APPLICANT

L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for Inalco SpA
315 East 68th Street #4-L
New York, NY 10021

4. BASIS FOR SUBMISSION
Pages 000001-000006 include a legal basis for submission. A suitability petition has also been filed.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Chronulac

7. NONPROPRIETARY NAME
Lactulose

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission	July 14, 1995
Refuse to File	August 17, 1995
Amendment	September 14, 1995
Refuse to File	October 23, 1995
Amendment	December 1, 1995
Acceptance	January 11, 1996

10. PHARMACOLOGICAL CATEGORY
Anti-constipation

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 17-884
DMF 11261
DMF (b) (4)
DMF 11262
DMF (b) (4)
DMF

13. DOSAGE FORM
Crystals for Constitution

14. POTENCY
10 g, 20 g

15. CHEMICAL NAME AND STRUCTURE
D- Fructose, 4-)-B-D-galactopyranosyl Lactulose

16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application contains several deficiencies.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is unapprovable.

19. REVIEWER: Karen A. Bernard, Ph.D.
DATE COMPLETED: 3/15/96

Following this page, 5 pages are withheld in full (b)(4).
Chemistry Review #1

cc: ANDA 74-712
DUP File
Division File
Field Copy

Endorsements:

HFD-645/K.Bernard/3/12/96/ K Bernard 5/8/96
HFD-645/B.Arnwine/4/25/96/ BJ Arnwine 5/10/96
x:\new\firmsam\inalco\ltrs&rev\74-712.naf
F/T by slm/3/29/96

DMF CHECKLIST FOR ANDA/AADA # 74-712 REVIEW #1

DMF #	TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	REVIEW COMPLETED
11261	II Lactulose Crystals, Inalco	1	sat	3/12/96

Comments: Reviewed by K. Bernard.

(b) (4)	II/ (b) (4)	I	sat	3/12/96

Comments: Reviewed by K. Bernard

11261	I	2		

Comments:

(b) (4)	I	2		

Comments:

(b) (4)	III (b) (4)	4		

Comments:

Comments:

Comments:

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no relevant revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").

Checklist page 1 of 1

. Karen Bernard
Reviewer

K Bernard
Signature

5/8/96
Date

1. CHEMIST'S REVIEW NO.2

2. ANDA # 74-712

3. NAME AND ADDRESS OF APPLICANT
L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for Inalco SpA
315 East 68th Street #4-L
New York, NY 10021

4. BASIS FOR SUBMISSION
All patents expired. No marketing exclusivity is associated with the reference listed drug. A suitability petition no. 92P-0370/CP 1 was approved 1/7/93.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Lactulose

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:

Original Submission	July 14, 1995
Refuse to File	August 17, 1995
Amendment	September 14, 1995
Refuse to File	October 23, 1995
Amendment	December 1, 1995
Acknowledgement receipt	January 11, 1996
Labeling review	March 19, 1996
Bio waiver granted	April 3, 1996
New Correspondence	May 8, 1996
Deficiency letter	May 15, 1996
Amendment	August 5, 1996

10. PHARMACOLOGICAL CATEGORY
Anti-constipation

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 17-884
DMF 11261
DMF (b) (4)
DMF 11262
DMF (b) (4)
DMF

13. DOSAGE FORM
Crystals Powder

14. POTENCY
10 g & 20 g

15. CHEMICAL NAME AND STRUCTURE

D- Fructose, 4-)-B-D-galactopyranosyl Lactulose

16. RECORDS AND REPORTS

The suitability petition for the 20 g unit dose packet was approved on April 19, 1996 (see new correspondence dated May 8, 1996).

17. COMMENTS

Method validation performed by the Northeast Regional Lab. found it not to be suitable for regulatory analysis.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend not approval letter to issue (Minor).

19. REVIEWER:

Edwin Ramos

DATE COMPLETED:

November 21, 1996

Edwin Ramos 1/10/97

Following this page, 6 pages are withheld in full (b)(4).
Chemistry Review #2

(b) (4)

[redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

A copy of the response to chemistry deficiency number 4 should be sent directly to the Northeast Regional Laboratory, Attn: Ella S. Walker.

Sincerely yours,

1/15/97

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

ANDA 74-712
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/ERamos
HFD-645/BArnwine
HFD-645/KSherrod KSherrod 1/14/97
HFD-640 /Division Director (final only) 1/13/97

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

DMF CHECKLIST FOR ANDA # 74-712 REVIEW #2

DMF #	TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	REVIEW COMPLETED
11262	II Lactulose Crystals, Inalco	1	Def	3/12/96

Comments: Reviewed by K. Bernard.

(b) (4)	II/ (b) (4)	1	sat	3/12/96

Comments: Reviewed by K. Bernard

(b) (4)

Comments:

(b) (4)

Comments:

(b) (4)

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;

(3) Reviewed previously and no relevant revision since last review;

(4) Sufficient information in application;

(5) Authority to reference not granted;

(6) DMF not available;

(7) Other (explain under"Comments").

Checklist page 1 of 1

Edwin Ramos
Reviewer

Signature

1/10/97
Date

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-712

3. NAME AND ADDRESS OF APPLICANT
L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for Inalco SpA
315 East 68th Street #4-L
New York, NY 10021

4. BASIS FOR SUBMISSION
All patents expired. No marketing exclusivity is associated with the reference listed drug. A suitability petition no. 92P-0370/CP 1 was approved 1/7/93.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Lactulose

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:

Original Submission	July 14, 1995
Refuse to File	August 17, 1995
Amendment	September 14, 1995
Refuse to File	October 23, 1995
Amendment	December 1, 1995
Acknowledgment receipt	January 11, 1996
Labeling review	March 19, 1996
Bio waiver granted	April 3, 1996
New Correspondence	May 8, 1996
Deficiency Letter	May 15, 1996
Amendment	August 5, 1996
Deficiency Letter	January 16, 1997
Amendment	May 23, 1997

10. PHARMACOLOGICAL CATEGORY
Anti-constipation

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 17-884
DMF 11261
DMF (b) (4)
DMF 11262
DMF (b) (4)
DMF
DMF

13. DOSAGE FORM
Crystals Powder

14. POTENCY
10 g & 20 g

15. CHEMICAL NAME AND STRUCTURE

D- Fructose, 4-)-B-D-galactopyranosyl Lactulose

16. RECORDS AND REPORTS

The suitability petition for the 20 g unit dose packet was approved on April 19, 1996 (see new correspondence dated May 8, 1996).

17. COMMENTS

Method validation performed by the Northeast Regional Lab. It was found to not be suitable for regulatory analysis. The field received the firm's response regarding the methods validation issues as per Ella Walker 6/3/97 (Northeast DO) The field will be picking up new samples and repeating the analysis based on the firm's response comments.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approval letter to issue (Minor).

19. REVIEWER: Karen Bernard

DATE COMPLETED: June 6, 1997

Following this page, 6 pages are withheld in full (b)(4). Chemistry Review #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-712 APPLICANT: Inalco S.p.A

DRUG PRODUCT: Lactulose for Oral Solution, 10 g and 20 g unit dose packets

The deficiencies below represent minor deficiencies.

A. Deficiencies:

Regarding the reconstitution study data you supplied for the Lactulose (b) (4), we ask that you repeat your analysis including testing for Assay and Related Substances. As previously requested, please determine the expected shelf-life of the reconstituted solution as well as the specification.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

Your methods were found to be not suitable for regulatory purposes. Based on the comments you provided to the district office, a new analysis of your methods is required. The application cannot be approved until the methods validation by the district office has been found satisfactory.

Sincerely yours,

6/18/97

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-712
DUP File
DIVISION FILE
Field Copy

Endorsements:

HFD-645/KBernard/6/7/97 K. Bernard 6/16/97
HFD-645/BArnwine/6/12/97 BJ concurs 6/17/97
HFD-645/KSherrod/6/12/97 KSherrod 6/17/97
HFD-640/FHolcombe/
X:\NEW\FIRMSAM\INALCO\LTRS&REV\74712NA.F
F/T by vlj/6/12/97

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

DMF CHECKLIST FOR ANDA # 74-712 REVIEW #3

DMF #	TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	REVIEW COMPLETED
11262	II Lactulose Crystals, Inalco	1	Def	3/12/96

Comments: Reviewed by K. Bernard.

(b) (4)	II/ (b) (4)	1	sat	3/12/96

Comments: Reviewed by K. Bernard

(b) (4)

Comments:

(b) (4)

Comments:

(b) (4)

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no relevant revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Checklist page 1 of 1.

Karen Bernard — Reviewer

K Bernard — Signature

6/16/97 — Date

1. CHEMIST'S REVIEW NO.4

2. ANDA # 74-712

3. NAME AND ADDRESS OF APPLICANT
L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for Inalco SpA
315 East 68th Street
New York, NY 10021

4. BASIS FOR SUBMISSION
All patents expired. No marketing exclusivity is associated with the reference listed drug. A suitability petition no. 92P-0370/CP 1 was approved 1/7/93.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Lactulose

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:

Original Submission	July 14, 1995
Refuse to File	August 17, 1995
Amendment	September 14, 1995
Refuse to File	October 23, 1995
Amendment	December 1, 1995
Acknowledgment receipt	January 11, 1996
Labeling review	March 19, 1996
Bio waiver granted	April 3, 1996
New Correspondence	May 8, 1996
Deficiency letter	May 15, 1996
Amendment	August 5, 1996
Deficiency Letter	January 16, 1997
Amendment	May 23, 1997
Deficiency Letter	June 19, 1997
Amendment	July 24, 1997
Amendment	July 30, 1997
T-Con	August 19, 1997
Telephone Amendment	September 4, 1997

10. PHARMACOLOGICAL CATEGORY
Anti-constipation

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 17-884
DMF 11261
DMF (b) (4)
DMF 11262
DMF (b) (4)
DMF

13. DOSAGE FORM
Crystals Powder

14. POTENCY
10 g & 20 g

15. CHEMICAL NAME AND STRUCTURE
D- Fructose, 4-)-B-D-galactopyranosyl Lactulose

16. RECORDS AND REPORTS
The suitability petition for the 20 g unit dose packet was approved on April 19, 1996 (see new correspondence dated May 8, 1996).

17. COMMENTS
Method validation performed by the Northeast Regional Lab. It was found to not be suitable for regulatory analysis. The field has received the firm's response regarding the methods validation issues as per Ella Walker 6/3/97 (Northeast DO) The field has analyzed new samples and repeated the analysis based on the firm's response comments. The methods are now satisfactory as of 8/21/97 by S. Yuen (Northeast DO).

This ANDA has been reviewed previously by another reviewer. This ANDA has been recommended for approval in accordance with OGD's PPG #29-90.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
September 5, 1997

Following this page, 6 pages are withheld in full (b)(4). Chemistry Review #4

cc: ANDA #74-712
Division File
Field Copy

Endorsements:

HFD-645/KBernard/9/5/97 KBernard 9/11/97
HFD-645/BArnwine/ALangowski/9/10/97 ALangowski for B. Arnwine 9/11/97
x:\new\firmsam\inalco\ltrs&rev\74712c3.apf
F/T by VLJ/9/11/97

Approvable

DMF CHECKLIST FOR ANDA # 74-712 REVIEW #4

DMF #	TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	REVIEW COMPLETED
11262	II Lactulose Crystals, Inalco	1	Sat	8/12/97

Comments: Reviewed by K. Bernard.

(b) (4)	II/ (b) (4)	1	sat	3/12/96

Comments: Reviewed by K. Bernard

(b) (4)

Comments: 4

(b) (4)

Comments: 4

(b) (4)

Comments: 4

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no relevant revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Checklist page 1 of 1

Karen Bernard — Reviewer

K Bernard — Signature

9/11/97 — Date

DIVISION REVIEW SUMMARY

ANDA: 74-712

DRUG PRODUCT: Lactulose (b) (4)

FIRM: L.S. Weiss and Company
U.S. Agent for Inalco SpA

DOSAGE FORM: Crystals for Oral Solution

STRENGTHS: 10 g and 20 g

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable as of June 12, 1997.

BIO INFORMATION: Biowaiver granted on 4/3/96.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
A. NEW DRUG SUBSTANCE

(b) (4)

Lactulose crystals are manufactured on (b) (4) Page 71 includes a table summarizing the lot numbers of bulk lactulose crystals, (b) (4) used in the production of unit dose pouches S05054 (10 g) and S05054 (20 g).

(b) (4)

The controls are described in DMFs # (b) (4) and #11262. COA's for the bulk crystals lot nos. S02054, S03054 and S05054 are included (pages 49, 60 & 72).

Lactulose Crystals Specifications (page 49)

(b) (4)

The finished product specifications are listed in Certificates of Analysis included for each of the lots # S02054-10, S02054-20, S03054-10, S03054-20, S05054-10, and S-05054-20.

(b) (4)

Analytical methods are referred to in DMF # (b) (4) The applicant acknowledges that the drug product is non-compendial, and additional specification test(s) may be required at a later date.

STABILITY

The post-approval stability protocol was revised to comply with FDA Stability Guidelines (page 309 and 5, dated 7/31/96). The first three production batches of each package size will be placed on stability and one batch annually, thereafter.

Accelerated (40°C & 75% RH) and 24 months of updated room temperature stability data for 3 lots of bulk crystals used in the final unit dose packages as well as the stability data on 10 g and 20 g unit dose packages are appended (amendment dated 8/5/96).

The applicant requested a (b) (4) expiry which was denied. Based on the stability data submitted, a 24 month expiry is granted. The firm acknowledges.

Stability Specifications

(b) (4)

The stability report forms included for the bulk and the unit dose packages (lot #'s S02054, S03054, and S05054) were revised to include: testing specification limits, testing dates, container closure information and drug substance or DMF starting material references.

LABELING-The labeling review was found satisfactory by A. Vezza on 6/2/97.

STERILIZATION VALIDATION - NA

SIZE OF EXHIBIT BATCHES-

Unit dose lactulose crystals are manufactured (b) (4) . The instructions and documentation for the manufacture of lactulose crystals (b) (4) respectively. Lactulose crystals are manufactured (b) (4) which is also manufactured (b) (4) Batch history information is recorded onto "run sheets" which are used to document critical phases of the production process. Copies of the blank "run sheets" are appended (page 85). The firm also claims that they will (b) (4) .

The manufacturing process is described in DMF #11262. Page 225 includes the Packaging and Labeling Procedures which are performed at (b) (4) . The master production record for the packaging and labeling of lactulose (b) (4) is included (page 226).

The packaging and labeling (executed) records for the demonstration batches are included (page 256). Lot #'s are S02054, S03054, and S05054 for 10 g and 20 g sizes. Lot nos. S02054, S03054 and S05054 were manufactured on 5/4/94, 5/5/94 and 5/9/94, respectively. A total of 10g/ (b) (4) units and 20 g/ (b) (4) were manufactured.

Lot #'s S020504, S030504, and S050504 were never manufactured, therefore run sheets were never made. The exhibit batch numbers are S02054, S03054 and S05054.

SIZE OF STABILITY BATCHES- A total of 10 g/ (b) (4) units and 20 g/ (b) (4) units were manufactured.

PROPOSED PRODUCTION BATCH- Same as above.

RECOMMENDATION: The application is approvable.

SIGNATURE: Karen Bernard
KBernard

DATE: September 11, 1997
9/11/97

1. CHEMIST'S REVIEW NO.5 (ADDENDUM TO REVIEW #4)

2. ANDA # 74-712

3. NAME AND ADDRESS OF APPLICANT
L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for Inalco SpA
315 East 68th Street
New York, NY 10021

4. BASIS FOR SUBMISSION
All patents expired. No marketing exclusivity is associated with the reference listed drug. A suitability petition no. 92P-0370/CP 1 was approved 1/7/93.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Lactulose

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:

Original Submission	July 14, 1995
Refuse to File	August 17, 1995
Amendment	September 14, 1995
Refuse to File	October 23, 1995
Amendment	December 1, 1995
Acknowledgment receipt	January 11, 1996
Labeling review	March 19, 1996
Bio waiver granted	April 3, 1996
New Correspondence	May 8, 1996
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Amendment	August 5, 1996
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Amendment	May 23, 1997
Deficiency Letter	June 19, 1997
Amendment	July 24, 1997
Amendment	July 30, 1997
T-Con	August 19, 1997
Telephone Amendment	September 4, 1997
Telephone Amendment	December 1, 1997

10. PHARMACOLOGICAL CATEGORY
Anti-constipation

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 17-884
DMF 11261
DMF (b) (4)
DMF 11262
DMF (b) (4)
DMF

13. DOSAGE FORM
Crystals Powder

14. POTENCY
10 g & 20 g

15. CHEMICAL NAME AND STRUCTURE
D- Fructose, 4-)-B-D-galactopyranosyl Lactulose

16. RECORDS AND REPORTS
The suitability petition for the 20 g unit dose packet was approved on April 19, 1996 (see new correspondence dated May 8, 1996).

17. COMMENTS
Method validation performed by the Northeast Regional Lab. It was found to not be suitable for regulatory analysis. The field has received the firm's response regarding the methods validation issues as per Ella Walker 6/3/97 (Northeast DO) The field has analyzed new samples and repeated the analysis based on the firm's response comments. The methods are now satisfactory as of 8/21/97 by S. Yuen (Northeast DO).

Also, on 12/1/97 the firm was requested to submit 1) a particle size specification for the drug product and 2) clarification regarding their assignment of related compounds specifications.

On 12/3/97 the firm faxed the requested information. The application is now approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
December 3, 1997

K Bernard 12/5/97

12/5/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-712

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE
PRE-ASSIGNMENT CHECK LIST FOR APPLICATIONS PENDING ASSIGNMENT

7/14
DATE: 7-19-95 (RP) 12-4-95

Application #: 74,717

SPONSOR: Inalco SpA

DRUG: Lactulose for Oral Soln 10g/Packet

DATE ASSIGNED TO REVIEWER: PDR

DIVISION QUEUE DATE:

YES (NO) 1. Is this a first time review by the Division for this Drug?

If Yes; The DBE, Director must be consulted before assignment is made, note comments by director below.

YES (NO) Is there another application pending and/or approved for the same drug, same manufacturer, but a different or same strength?

If Yes; This application should be assigned to the same reviewer, note related applications below.

YES (NO) Is this a drug product that is pre-assigned to a specialized reviewer.

YES NO Is there a conflict of interest with this review?

DBE, personnel that have a conflict of interest, with this application.
1.
2.
3.
4.

cc: Orig
Div
HFD-650 Random Assignment File

JA1

Vet Biol
in DocR

rvg MKP 3/7/96

MAR 27 1996

Lactulose (b) (4)

10 g/pouch

ANDA #74-712

Reviewer: Moo Park

Filename: 74712W.795

Inalco

Milano, Italy

Submission Date:

July 14, 1995

Review of a Waiver Request

I. Objective

Review of Inalco's waiver request for its Lactulose (b) (4), 10 g/pouch. The reference product is Marion Merrell Dow's Chronulac^{R} (Lactulose Solution), 10 g/15 mL. Lactulose is a colonic acidifier which promotes laxation.

II. Comments

1. Inalco (US agent: Bennett and Co., Clarksville, MD) received approval on suitability petition (Docket #92P-0370/CP 1) on Lactulose (b) (4), 10 g/pouch, as a new dosage form. The content of the pouch is dissolved in water immediately prior to administration.

2. The test product contains only lactulose crystal. Request for waiver of *in vivo* bioequivalence study is granted.

3. To reviewers in Chemistry and Labeling: No procedure was included for proper reconstitution in the package insert. The master batch record does not show any information on formulation or procedure.

III. Recommendation

The Division of Bioequivalence agrees that the information submitted by Inalco demonstrate that Lactulose (b) (4), 10 g/pouch, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study requirements for the test product for ANDAs #74-712 is granted. The Division of Bioequivalence deems Inalco's Lactulose (b) (4), 10 g/pouch, to be bioequivalent to Maion Merrell Dow's Chronulac^{R}, 10 g/15 mL.

The firm should be informed of the recommendation and reviewers in Chemistry and Labeling should be informed of comment #3.

Moo Park

Moo Park, Ph.D.
Chemist, Review Branch III

Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE Ramakant M. Mhatre 3/27/96
Ramakant M. Mhatre, Ph.D.
Branch Chief, Review Branch III
Division of Bioequivalence

K/D See Memo
Concur: RPC 3, 95 10/ Date: _____
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-712 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Park), Drug File, Division File

File history: Draft(3/8/96); Final(3/26/96)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Lactulose (b) (4)	Inalco
10 g/pouch	Milano, Italy
ANDA #74-712	Submission Date:
Reviewer: Moo Park	July 14, 1995

REF PRODUCT	Marion Merrell Dow's Chronulac® (Lactulose Solution), 10 g/15 mL. AA Drug Product
BE STUDY DESIGN	n/a
STUDY RESULTS	n/a
WAIVER	Waiver granted.

INITIAL: Moo Park DATE: 9/19/97
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: R M Mhatre DATE: 9/19/97
TEAM LEADER: Ramakant M. Mhatre, Ph.D.
BRANCH: III

INITIAL: R Patnaik DATE: 10/17/97
DIRECTOR: Rabindra Patnaik, Ph.D.
DIVISION OF BIOEQUIVALENCE
Acceptable under 320.24(b)(6)

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-712

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

inalco

Labeling Review Completed 3/14/96 DLincoln

Refuse to file 7/21/95

7/26/95

DATE JUL 14 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: Original Abbreviated New Drug Application
Lactulose (b) (4) 10 and 20 grams unit dose
One Volume

Dear Sir or Madame:

Attached to this cover letter is an original abbreviated new drug application for lactulose (b) (4) packaged in unit dose pouches of 10 grams and 20 grams. This product was the subject of a suitability petition (92P-0370/CP 1), approved by the Agency on January 7, 1993 (copy enclosed).

Lactulose crystals are manufactured (b) (4) in our bulk pharmaceutical facility in (b) (4) The purpose of this application is to provide for the packaging of a portion of the bulk crystals production into unit dose pouches. The packaging operation will be performed by a contractor located within the United States.

This application relies heavily on several drug master files which describe the bulk pharmaceutical facility, the manufacture of the (b) (4) and crystals, as well as the packaging subcontractor and packaging components. A list of all the drug master files referenced in this application is attached in Section XXI.

Thank you for your attention to this submission. If you have any questions, you may contact me or our U.S. agent:

L. Steve Weiss
L.S. Weiss & Company
315 E. 68th Street
New York, New York 10021
212/288-3808 phone
212/517-3856 fax

RECEIVED

JUL 19 1995

GENERIC DRUGS

Sincerely,

G. Cipolletti

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

INALCO S.P.A.
VIA CALABIANA 18
MILAN 20139

ANDA #: N074712

Dear Sir/Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the following:

NAME OF DRUG:
LACTULOSE (b) (4) , for Oral Solution
Dosage Form: ~~PDR~~ Potency: 10 G/PACKET,20G/PACKET USP:

DATE OF APPLICATION: 14-JUL-95

DATE OF RECEIPT: 19-JUL-95

We will correspond with you further after we have had the opportunity to review the application.

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

amount
Randomized
HFD-645

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-712

L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for: Inalco SpA
315 East 68th Street, #4-L
New York, NY 10021

AUG 17 1995

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated July 14, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Lactulose for Oral Solution, 10 g and 20 g unit dose packets.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

Your Suitability Petition (92P-0370/CP 1) was approved for a 10 gram unit dose packet only. Please withdraw all references to the 20 gram unit dose packet.

You have failed to provide a certification that the third (field) copy of the application has been submitted to the Agency and that it is a "true" copy of the technical sections of the application. Foreign applicants should submit the third (field) copy to the Office of Generic Drugs. Refer to Sections 314.94(d)(5) and 314.440 of the Final Rule, published in the Federal Register, September 8, 1993, pages 47351 and 47352. Please provide this certification with your third copy.

You have failed to provide certifications of compliance with Current Good Manufacturing Practices (CGMP) for the applicant, Inalco SpA, or the manufacturing facility, INFRA SrL. Please provide these certifications.

You have failed to designate on your blank Master Batch Record the largest batch size intended for production. Please be aware that approval cannot be given for more than a ten-fold scale up of the exhibit batch. Please revise your Master Batch Record to reflect this maximum batch size intended for production.

While you have provided packaging records, the lack of a clearly designated yield on your exhibit batch records prevents a determination of complete packaging of the exhibit batches. Please provide documentation of the yield and that it was completely packaged in accordance with Policy and Procedure Guides 22-90 and 41-95 and letters to the industry dated November 8, 1991, and August 4, 1993.

You must provide an environmental assessment under 21 CFR Section 25.31. You may be eligible for a categorical exclusion under 21 CFR Section 25.24(c)(1). In addition, please provide a certification of compliance with all applicable environmental laws.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, the Form FDA 356h submitted in the archival copy of the application lacks an original signature. Please provide this form with an original signature.

Also, while we note you did provide a side-by-side comparison of the package insert for your proposed drug product with the reference listed drug, you failed to provide a side-by-side comparison between the container labels of your proposed drug product with the reference listed drug. Please provide this comparison with all differences **annotated** and explained.

Also, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

Jerry Phillips 8-17-95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-712
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Atg Chief 7/31/95 date
HFD-615/WRussell, CSO 7/27/95 date
HFD-610/YRMille, Chief, LRB (for YRM) 8/1/95 date
HFD-645/BArnwine, Sup. Chem. date 8/2/95
WP File\A:\rtfanda\74-712
F/T File hrw 7-27-95
ANDA Refuse to File!

Bennett and Company

13560 BRIGHTON DAM ROAD
CLARKSVILLE, MARYLAND 21029
(301) 854-2046
FAX (301) 854-3908

FDA - CONSULTANTS
MARTHA M. BENNETT
DEAN A. BARLOW

August 21, 1995

Dockets Management Branch
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

Citizen Petition

The undersigned submits this Petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to accept the submission of an abbreviated new drug application for a new drug which has a different dosage form from the listed drug.

A. Action Requested

The undersigned requests permission to file an abbreviated new drug application for lactulose crystals in a 20 gram unit dose pouch. The Agency previously approved a suitability petition (92P-0370/CP 1) for this dosage form, packaged in a 10 gram unit dose pouch. A copy of the approval letter for this petition is attached for your reference.

Lactulose crystals are to be reconstituted with water by the patient to form a liquid for oral administration. The dosage form of the listed drug product, Chronulac (NDA # 17-884, Merrell Dow) is a liquid.

B. Statement of Grounds

The proposed drug product meets the criteria for submission of an abbreviated new drug application as described in section 505(j)(2)(C)(i) of the Federal Food, Drug, and Cosmetic Act.

The proposed drug product and the listed drug product contain the same active ingredient at the same strength and, when ingested, are the same dosage form. This Petition seeks permission to submit an ANDA for a dried form (crystals) of the listed drug product. Prior to use, the patient will reconstitute the crystals with water for oral administration as a liquid, in the same form as the listed drug product.

Since the proposed drug product and the listed drug product would be identical in active ingredient, strength, and route of administration, the safety and effectiveness of the proposed drug product is not expected to be different from that of the listed drug product.

The labeling for the proposed drug product, including dosage and administration, will be consistent with the most recently approved labeling for the listed drug product. Copies of the draft labeling and approved labeling are attached.

C. Environmental Impact

The undersigned claims a categorical exclusion for submission of an environmental assessment in accordance with 21 CFR 25.24(c)(1). This claim is based upon the fact that the proposed drug product has a chemical structure and composition with known pharmacological properties and indications for use that are identical to a drug product which is already being marketed.

D. Economic Impact

A statement concerning the economic impact of the requested action will be supplied at the request of the Commissioner.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petitioner relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Sincerely,

Martha M. Bennett

Martha M. Bennett

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Bennett and Company
Attention: Martha M. Bennett
13560 Brighton Dam Road
Clarksville, Maryland 21029

Docket No. 92P-0370/CP 1

Dear Madam:

This is in response to your petition filed on September 22, 1992, requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug product: Lactulose (b) (4), 10 g/ packet. The drug product to which you refer in your petition is Chronulac (Lactulose Syrup USP, 10 g/15 mL), manufactured by Marion Merrell Dow Inc.

We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act), and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced product.

Your request involves a change in dosage form from that of the listed reference drug product (i.e. from liquid to crystals). The type of change you request is the type of change authorized under the Act.

Under Section 505(j)(2)(C)(i) of the Act the Agency must approve petitions seeking a change in dosage form which differs from the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing dosage form.

The Agency has determined that a change in dosage form (i.e., from liquid to crystals) for this specific product does not pose questions of safety or effectiveness and concludes, therefore, that investigations are not necessary in this instance. The basis for this determination is that the uses, dose, strength and route of administration of the proposed product are the same as those of the listed reference drug product. In addition, if shown to meet the bioavailability requirements, the proposed product can be expected to have the same therapeutic effect as the listed reference drug product. Therefore, an ANDA may be submitted for the listed referenced product.

The approval of this petition to allow an ANDA to be submitted for the above-referenced product does not mean that the Agency has determined that an ANDA will be approved for the product. The determination that an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

To permit review of your ANDA submission you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved, the product will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A) of the Act. We suggest that you contact the Director, Division of Bioequivalence at (301) 295-8290 to determine the specific requirements for this product. During the review of your application, the Agency may require the submission of additional information.

The listed drug product to which you refer in your ANDA must be the one upon which you based this petition. In addition, you should refer in your ANDA to the petition docket number above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, HFD-305, Room 1-23 of the Park Building, 12420 Parklawn, Drive, Rockville, MD 20857.

Sincerely yours,

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

inalco

Ozz

Returned to file 10/3/95

September 14th, 1995

Jerry Phillips, Acting Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

DR. Label
NDA ORIG AMENDMENT
AC

Re: ANDA 74-712
Lactulose (b) (4)

Dear Sir,

This letter is in response to your letter of August 17,1995 (copy attached), in which you requested that additional information be submitted to this abbreviated new drug application for lactulose (b) (4)

We have attached the information you requested. In each of the sections which follow this cover letter, we have repeated each of your requests and enclosed our responses.

Thank you for your prompt attention to this filing. If you need additional information, please let us know.

Sincerely,

G. Cipolletti

RECEIVED
SEP 18 1995
GENERIC DRUGS

PAGE 1
09/14/95

ANDA 74-712

L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for: Inalco SpA
315 East 68th Street, #4-L
New York, NY 10021

OCT 23 1995

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated July 14, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Lactulose for Oral Solution, 10 g and 20 g unit dose packets.

Reference is also made to our "Refuse to File" letter dated August 17, 1995, and your amendment dated September 14, 1995.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> Until a suitability petition is approved for the 20 gram unit dose configuration, the application cannot be filed.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

Jerry Phillips 10/23/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-712
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett
Endorsement: HFD-615/PRickman, Acting Chief 10/17/95 date
HFD-615/WRussell, CSO 10/4/95 date
HFD-610/CHoppes, Chief, LRB 10/19/95 date
HFD-645/BArnwine, Sup. Chem 10/19/95 date
WP File\russell\74\74-712
F/T by Fox 10/4/95
ANDA Refuse to File!

uffici: via calabiana, 18 - 20139 milano
tel. 55213005 r.a.

telefax 5694518
telex 332127 inal-i / 324101 inalc-i
telegrammi Inalco Milano
capitale sociale 2.100.000.000 i.v.
c.c.i.a.a. n. 832900 milano
tribunale milano n. 150119 - 3704 - 19
meccanografico MI 032579
c/c postale n. 31404205
codice fiscale 00861350155
partita i.v.a. IT 00861350155

505(j)(2)(A) complete
for filing
12/5/95

Jerry Phillips, Acting Director
Division of Labeling & Program Support,
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place MPN2
Rockville, Maryland 20855

MILANO, December 1st, 1995 VS. RIF. NS. RIF.

Re: ANDA 74-712
Lactulose (b) (4)

NDA ORIG AMENDMENT AC

Dear Sir,

I am writing in response to your "Refuse to File" letter of October 23, 1995.

Inasmuch as we have not yet received the approval letter for the suitability petition for the 20 gram unit dose configuration, we are withdrawing references to this package size in our application. We plan to amend the application to include this package size after the approval letter is received.

We hope that this withdrawal will remove all existing impediments to the filing and review of this application.

Thank you in advance for your attention to this matter.

Sincerely,

G. Cipolletti

RECEIVED
DEC 04 1995
GENERIC DRUGS

ANDA 74-712

L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for: Inalco SpA
315 East 68th Street, #4-L
New York, NY 10021

JAN 11 1996

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letters dated August 17, 1995 and October 23, 1995; and your amendments dated September 14, 1995, and December 1, 1995.

NAME OF DRUG: Lactulose for Oral Solution, 10 g unit dose packets

DATE OF APPLICATION: July 14, 1995

DATE OF RECEIPT: July 19, 1995

DATE ACCEPTABLE FOR FILING: December 4, 1995

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Consumer Safety Officer
(301) 594-1300

Sincerely yours,

Jerry Phillips 1/11/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-712
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB 12/22/95 date
HFD-615/WRussell, CSO 12/19/95 date
HFD-645/BArnwine,Sup. Chem. 12/21/95 date
WP File\X:\NEW\firmsam\LSWeiss\ltrs&rev\74-712.f
F/T hrw 12-06-95
ANDA Acknowledgement Letter!

ANDA 74-712

APR - 3 1996

L.S. Weiss and Company.
Attention: L. Stephen Weiss
U.S. Agent for: Inalco SpA
315 East 68th Street, #4-L
New York NY 10021

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Lactulose for Oral Solution, 10 g unit dose packets.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-712, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
Letter Out, Bio Acceptable

Endorsements:

M. Park
R. Mhatre
J. Gross

DRAFTED: 03/29/96 STM X:\WPFILE\BIO\FINAL\N74712.APP

L.S.WEISS & CO,INC.

file KC 6/18/96

May 8, 1996

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP N C

Re: ANDA 74-712, Lactulose (b) (4)
Amendment

Dear Sir,

The purpose of this submission is to amend our original ANDA for lactulose (b) (4) which was filed December 4, 1995. We request that the Agency consider for approval the 20 Gram unit dose packet which was fully described in our original submission.

Filing of the original application was initially refused because there was no approved suitability petition for the 20 gram unit dose packet. In response to the "refuse to file letter", we requested that the Agency review the application based on the 10 gram unit dose packet and consider references to the 20 gram unit dose withdrawn until a suitability petition was approved. The application was then filed.

The suitability petition for the 20 gram unit dose packet has been approved. A copy of the letter is attached.

As stated above, complete information describing the 20 gram unit dose packet was included and filed in the original submission. This includes labeling, description of packaging components, master and batch production packaging records, and stability data. A copy of the Table of Contents is attached for your reference and to assist you in locating the information related to the 20 /gram unit dose packet.

If you have any questions regarding this amendment or need additional information, please give me a call at 212/288-3808.

RECEIVED
MAY 09 1996
GENERIC DRUGS

Sincerely,

L. Stephen Weiss, President
L.S. Weiss & Co., Inc.
US Agent for Inalco SpA

315 E. 68 ST., NEW YORK, NY 10021 • (212) 288-3808 • FAX (212) 517-3856 • TLX: 295576 WEIS UR

Marked 5-30-96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Bennett and Company
Attention: Martha M. Bennett
13560 Brighton Dam Road
Clarksville, Maryland 21029

APR 19 1996

Docket No. 95P-0287/CP1

Dear Madam:

This is in response to your petition filed August 23, 1995, requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug product: Lactulose (b) (4) 20 g/ packet. The drug product to which you refer in your petition is Chronulac (Lactulose Syrup USP, 10 g/15 mL), manufactured by Marion Merrell Dow Inc.

We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act (Act), and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced product.

Your request involves a change in dosage form from that of the listed reference drug product (i.e., from syrup to crystals). In addition, you also request a change in strength from that of the listed drug (i.e., from 10 g/15 mL to 20 g/packet). The types of changes you request are the types of changes authorized under the Act.

Under Section 505(j)(2)(C)(i) of the Act the Agency must approve petitions seeking a change in dosage form or strength which differs from the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing dosage form or strength.

The Agency has determined that changes in dosage form (i.e., from syrup to crystals) and strength (i.e., from 10 g/15 mL to 20 g/packet) for this specific product do not pose questions of safety or effectiveness and has concluded, therefore, that investigations are not necessary in this instance. The basis for this determination is that the uses, and route of administration of the proposed product are the same as those of the listed reference drug product. In addition, the dose of the proposed product falls within the dosage range established in the approved labeling of the listed reference drug product. Further, if shown to meet the bioavailability requirements, the proposed product can be expected to have the same therapeutic effect as the listed reference drug product. Therefore, an ANDA may be submitted for the above-referenced product.

The approval of this petition to allow an ANDA to be submitted for the above-referenced product does not mean that the Agency has determined that an ANDA will be approved for the product. The determination that an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

To permit review of your ANDA submission you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved the product will, among other things, be required to meet current bioavailability requirements under Section 505 (j) (2) (A) of the Act. We suggest that you contact the Director, Division of Bioequivalence at (301) 594-2290 to determine the specific requirements for this product. During the review of your application the Agency may require the submission of additional information.

The listed drug product to which you refer in your ANDA must be the one upon which you based this petition. In addition, you should refer in your ANDA to the petition docket number above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, HFA-305, Park Building, 12420 Parklawn, Drive, Room 1-23, Rockville, MD 20857.

Sincerely yours,

Gordon R. Johnston for /

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-712

L.S. Weiss and Company
Attention: L. Stephen Weiss
U.S. Agent for Inalco, S.p.A.
315 East 68th Street, #4-L
New York, NY 10021

MAY 15 1996

Dear Mr. Weiss:

This is in reference to your abbreviated new drug application dated July 14, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lactulose for Oral Solution, 10 g unit dose packets.

Reference is also made to your amendment dated December 1, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. The application cannot be approved until deficiencies regarding DMF #11262 have been addressed satisfactorily by the holder.

2. Page 83 includes the name of the packaging facility, (b)(4), however, there is no address listed. Please supply the packaging firm's address.

3. Regarding the executed run sheets included in the ANDA for the manufacturing process, you should include run sheets for the exhibit batches for lot #'s S020504, S030504, and S050504.

4. You should be advised that since the drug product is non-compendial, the finished drug product specification tests are under review by the agency. The addition of further specification test(s) may be required at a later date. Also, samples of the drug product will be obtained by our district laboratory staff for analytical methods validation.

5. Regarding your stability protocol, you are requested to commit to placing the first three production batches on stability and one annually, thereafter.

6. Based upon the stability data submitted, please be advised that at this time your request for a (b) (4) expiration dating period is denied. We will grant a 2 year expiration dating period at the time of approval. In order to receive a (b) (4) expiry, you would be required to submit of room temperature stability data.

7. Also, with regard to the stability report forms included for the bulk and the unit dose packages (lot #'s S02054, S03054, and S05054), the following information should be included on the report form: testing specification limits, testing dates, container closure information and drug substance or DMF starting material references.

B. Labeling Deficiencies:

1. GENERAL COMMENTS

a. Please revise the established name on your labels and labeling to read "Lactulose for Oral Solution" rather than "Lactulose (b) (4) ".

b. Provide specific instructions on the preparation of a dose. Please address these issues:

- Should the patient or provider be further cautioned against consuming the dry form, rather than just "... should be dissolved in water immediately prior to administration"?
- What volume of fluid is desirable to mix a dose with?
- Can the product be mixed in fluids other than water?
- What does one do when a larger dose is prepared and multiple packets are used?
- Please note that the usual dosage is 10 to 20 grams. How does a patient or provider prepare an intermediate dose (i.e., 15 g)?
- Please state if the resulting solution has a color or is it colorless?

Revise your labels and labeling accordingly.

c. You are required to obtain an NDC number for your product and you are encouraged to include it on your labels and labeling. See 21 CFR 207.35 for further guidance.

2. CONTAINER - 10 g packet

a. Relocate "10 grams" to follow the established name and use "Single Dose Packet" rather than "(b) (4) .

b. Revise the "Contents" statement to read "Each packet contains 10 grams lactulose (and less ..."

c. Delete the statement (b) (4) , see accompanying package insert." and revise the "Usual Adult Dose" statement to read:

> Usual Adult Dosage: (b) (4) daily. See accompanying package insert.

d. If room permits, include the storage recommendation statement.

e. See GENERAL COMMENTS above.

3. CARTON

a. See GENERAL COMMENTS above.

b. Relocate "10 grams" to follow the established name and use (b) (4) Single Dose Packets" rather than "(b) (4) .

c. Revise the "Each 10 grams" statement to read:

> Each packet contains 10 grams lactulose and less than 0.3 g of galactose and lactose as a total sum.

d. Include the storage recommendation statement.

e. Revise the "Indications and Usage" section to read as follows:

> Indications: For the treatment of constipation. See accompanying package insert.

f. Delete the statement "(b) (4) see accompanying package insert." and revise the "Usual Adult Dose" statement to read:

> Usual Adult Dosage: (b) (4) daily. See accompanying package insert.
>
> Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce a normal bowel movement.

4. INSERT

a. DESCRIPTION

i. First paragraph, third sentence - Include the pH range of the resultant solution when mixed according to directions.

ii. 4-*O*-β-D-Galactopyranosyl ... [italic "*O*" and capital "G"]

iii. Include the molecular formula.

b. CLINICAL PHARMACOLOGY

First paragraph, third sentence - ... amounts of formic and acetic acids, ... [delete (b) (4)].

c. INDICATIONS AND USAGE

Revise the first paragraph to read:

> Lactulose for Oral Solution is indicated for the treatment of constipation. In patients ...

d. CONTRAINDICATIONS

Revise to read:

Since Lactulose for Oral Solution contains galactose ...

e. PRECAUTIONS

i. General - See comment d, CONTRAINDICATIONS.

ii. Pediatric Use - Use "pediatric patients" rather than "(b) (4)".

f. OVERDOSAGE

Signs and Symptoms, second sentence - "symptoms" [plural].

g. DOSAGE AND ADMINISTRATION

i. First paragraph - Revise to read:

The usual adult dosage is 10 g to 20 g (b) (4) of lactulose daily. The dose may be increased to 40 g (b) (4) daily if necessary. Twenty-four ...

ii. See comment b under GENERAL COMMENTS.

h. HOW SUPPLIED

i. See comment c under GENERAL COMMENTS.

ii. Delete reference to the "20 g (b) (4) pouch" and revise to include the established name, dosage form and container size. For example:

Lactulose for Oral Solution is available in 10 g single dose packets in cartons of (b) (4)

iii. Revise the storage recommendation to read:

Store at room temperature 15°-30°C (59°-86°F).

iv. We encourage the inclusion of the "Caution: Federal law ..." statement.

i. Per 21 CFR 201.56(e), place the revision date prominently immediately following the last section of the insert.

Please revise your container label and carton and insert labeling, as instructed above, and submit draft labels and labeling.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a)(8)(iv), please provide a side-by-side comparison with your last submission.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

5/15/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-712
DUP File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-645/K.Bernard/3/12/96/ K Bernard 5/8/96
HFD-613/D.Konigstein/4/1/96/ D Konigstein 5/8/96
HFD-617/K.Sherrod/3/26/96/ K Sherrod 5/10/96
HFD-645/B.Arnwine/4/25/96/ (BJ per concurrence) 5/10/96
x:\new\firmsam\inalco\ltrs&rev\74-712.naf F Phillips 5/9/96
F/T by slm/3/29/96

NOT APPROVABLE: MAJOR AMENDMENT

NDA ORIG AMENDMENT
N/A draft

L.S. WEISS & CO, INC.

August 5, 1996

Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
AUG 0 8 1996
GENERIC DRUGS

RE: ANDA 74 - 712, Lactulose (b) (4)
Major Amendment

Dear Sir:

As the US Agent for Inalco S.p.A., I am filing this amendment in response to your letter of May 15, 1996 in which the chemistry and labeling deficiencies were identified. This package contains our itemized responses to each of the deficiencies noted.

If you have any questions regarding this information, please give me a call.

Sincerely,

L. S. Weiss & Co., Inc.

L. Stephen Weiss

LSW:er
encl.

271 MADISON AVE., NEW YORK, NY 10016 • (212) 288-3808 • FAX (212) 517-3856 • TLX: 295576 WEIS UR

MINOR AMENDMENT

JAN 16 1997

ANDA/~~AADA~~: 74-712

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT L.S. Weiss + Co Agent for PHONE (212) 288-3808
ATTN: L. Stephen Weiss FAX (212) 517-3856

FROM: Kassandra Sherrod PROJECT MANAGER (301-594-1300)

Dear Sir/~~Madam~~:

This facsimile is in reference to your abbreviated new drug/ antibiotic application dated July 14, 1995, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Lactulose for Oral Solution, 10g and 20g packets.

Reference is also made to your amendment(s) dated May 8 and August 5, 1996

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactiveated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/~~will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing. For further clarification or assistance please contact the Project Manager listed above.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.min

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-712 Date of Submission: August 5, 1996

Applicant's Name: **Inalco SpA**

Established Name:
Lactulose for Oral Solution, 10 g and 20 g single dose packets

Labeling Deficiencies:

1. GENERAL COMMENT

   We remind you that when draft labeling is submitted, four copies of each item are required.

2. CONTAINER - 10 g and 20 g Single Dose Packets

   a. We encourage you to differentiate your product strengths by the use of contrasting colors, boxing, or some other means.

   b. Usual Adult Dosage - Revise to read:

      10 to 20 grams daily. See accompanying package insert.

   c. Revise "Directions" to read "Directions for Preparation" and revise to read:

      Dissolve contents of packet in half a glass (4 ounces) of water.

3. CARTON - (b) (4) (10 g and 20 g)

   a. See comments under Container.

   b. Is the unit-dose package child-resistant? If it is not, include the statement "This unit-dose package is not child-resistant."

   c. 10 g - Store ... 15°-30°C (59°-86°F). [°C first]

4. INSERT

   a. DESCRIPTION

      Paragraph 1

i. Sentence 2 - Delete the comma after "galactose."

ii. Delete the last two sentences "The pH .. (b) (4) "

b. PRECAUTIONS

General, paragraph 1 - Revise to read "... than 0.3 g/10 g as a total sum), it ..."

c. DOSAGE AND ADMINISTRATION

i. Paragraph 1

Delete " (b) (4) in the first and second sentences, respectively.

ii. Insert the subsection heading "Directions for Preparation" after the first paragraph.

iii. Paragraph 2 - Revise to read:

Dissolve contents of packet in half a glass (4 ounces) of water.

iv. We acknowledge your proposal regarding intermediate dosages, however, upon further review, we find your original proposed draft acceptable without this information. Please delete paragraph 3.

v. Regarding the color of the resultant solution: You indicate it "may" have a slightly pale yellow color. Could it be colorless? If not, it would be appropriate to indicate that it "has" a slightly pale yellow color". If so, "... may be colorless to a slightly pale yellow color" would be more descriptive. Please comment and/or revise.

d. HOW SUPPLIED

We encourage the inclusion of the "Caution: Federal law ..." statement in this section.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container (packet) labels and carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Adolph Vezza / for J. Phillips

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Following this page, 1 page is withheld in full (b)(4).
Chemistry comments to the applicant dated 1/16/97.

(b) (4)

[redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

A copy of the response to chemistry deficiency number 4 should be sent directly to the Northeast Regional Laboratory, Attn: Ella S. Walker.

Sincerely yours,

1/15/97

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

inalco s.p.a.

uffici: via calabiana, 18 - 20139 milano
tel. 02-55213005 r.a. - telefax 02-5694518

telex 332127 inal-i / 324101 inalc-i
telegrammi Inalco Milano
cap. soc. £. 3.000.000.000 delib., £. 2.800.000.000 vers.
registro delle imprese di milano n. 150119
R.E.A. di milano n. 832900
meccanografico MI 032579
c/c postale n. 31404205
codice fiscale 00861350155
partita i.v.a. IT 00861350155

Jerry Phillips, Acting Director
Division of Labeling & Program Support,
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place MPN2
Rockville, Maryland 20855

MILANO, April 24th, 1997 VS. RIF. NS. RIF.

Ref.: ANDA 74-712
Lactulose for Oral Solution 10 g and 20 g single dose packets

---

Dear Mr. Phillips,

we are writing in response to the Labeling Deficiency Letter dated January 16th, 1997.

As for your instructions mentioned in your a.m. letter we have reviewed our labels and labeling and we are submitting the requested 12 copies.

We hope that our review is satisfactory.
If you need any further changes, please let us know.

Sincerely,

Giovanni Cipolletti
INALCO S.p.A.

c.c Mrs. Kassandra Sherrod
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

STEVE WEISS & CO., INC.

May 23, 1997

TPL - Satisfactory for approval labeling summary dtd 5/30/97 draft attached

NDA ORIG AMENDMENT

Frank O. Holcombe, Jr., Ph.D
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-712, LACTULOSE (b) (4)
MINOR AMENDMENT

Dear Sir:

As the US Agent for Inalco S.P.A. I am filing this **MINOR** amendment in response to your letter of **January 16, 1997** in which the chemistry and labeling deficiencies were identified. This package contains our itemized response to each of the deficiencies noted.

If you have any questions regarding this information, please give me a call.

Sincerely,

STEVE WEISS & CO., INC.

Steve Weiss, Pres.

Encl: 3 complete sets:

- Method Validation For The Assay Of Related Substances in Lactulose (b) (4)
- Method Validation For The Assay Of Related Substances in (b) (4)
- Method Validation For The Assay Of Lactulose In Lactulose Syrup
- Method Validation For The Assay Of Lactulose In Lactulose (b) (4)
- (b) (4) Analytical Methods *
- Lactulose (b) (4) Analytical Methods*
- Chemistry Comments To ANDA 74-712 MINOR Amendment (7 pages)*
- FDA Form 3499
- Cartons: 1, 50X10 Gm; 1, 50X20 Gm; Unfilled packets; package inserts
- copy of cover letter to North East Regional Laboratory (attn: Ms. Ella Walker) for * attachments
- Copy of cover letter to Jerry Phillips. (Original cartons to Jerry Phillips).

CC: Mrs. Kassandra Sherrod, OGD, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 - 2773

RECEIVED
MAY 27 1997
GENERAL

Madeline 5-28-97

315 E. 68 ST., NEW YORK, NY 10021 • (212) 288-3808 • FAX (212) 517-3856 • TLX: 295576 WEIS UR

JUN 19 1997

MINOR AMENDMENT

ANDA: 74-712

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Appears this way on original.

Center for Drug Evaluation and Research
FDA

TO: APPLICANT U.S. Agent for: Inalco SpA PHONE (212) 288-3808
Steve Weiss & Co., Inc.
ATTN: Steve Weiss FAX 212 517 3856

FROM: Kassandra Sherrod, PROJECT MANAGER (301-594-1300)

Dear Sir~~/Madam~~:

This facsimile is in reference to your abbreviated new drug application dated July 14, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lactulose for Oral Solution 10g and 20g single dose packets.

Reference is also made to your amendment(s) dated May 23, 1997.

The application is deficient and, therefore not approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactiveated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been~~/will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.min

JUN 19 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-712 APPLICANT: Inalco S.p.A

DRUG PRODUCT: Lactulose for Oral Solution, 10 g and 20 g unit dose packets

The deficiencies below represent minor deficiencies.

A. Deficiencies:

Regarding the reconstitution study data you supplied for the Lactulose (b) (4), we ask that you repeat your analysis including testing for Assay and Related Substances. As previously requested, please determine the expected shelf-life of the reconstituted solution as well as the specification.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

Your methods were found to be not suitable for regulatory purposes. Based on the comments you provided to the district office, a new analysis of your methods is required. The application cannot be approved until the methods validation by the district office has been found satisfactory.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

VS noted 8/5/97

STEVE WEISS & CO., INC.

July 30, 1997

AMENDMENT

N/AM

Frank O. Holcombe, Jr., Ph.D
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-712, LACTULOSE (b) (4)
MINOR AMENDMENT

Dear Sir:

As the US Agent for Inalco S.P.A. I am filing this **MINOR** amendment in response to your letter of **JUNE 16, 1997** in which certain deficiencies were identified. This package contains:

- our response to **38.A**. additional data regarding reconsitiution studies (3 sets)
- **38. B:** copies of the cover letter to FDA Northeast Regional Laboratory for samples and additional copies of the analytical procedures

If you have any questions regarding this information, please give me a call.

Sincerely,

STEVE WEISS & CO., INC.

Steve Weiss, President

cc: Mrs. Kassandra Sherrod, OGD, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 - 2773

RECEIVED
AUG 01 1997
GENERIC DRUGS

Nadini 8/5/97

315 E. 68 ST., NEW YORK, NY 10021 • (212) 288-3808 • FAX (212) 517-3856 • TLX: 295576 WEIS UR

RECORD OF TELEPHONE CONVERSATION
Re: Remaining issues of Methods Validation

I called Mr. Weiss at the request of the team leader. ANDA #74-712 is now approvable, except for the field laboratory comments to the firm. The methods validation were repeated by the field and found to be satisfactory as per Stella Yuen of the Northeast Regional Laboratory, however the firm was requested to address the fact that the assay test and the related substances test do not include a system suitablity requirement. I explained to Mr. Weiss that this issue must be addressed before the ANDA can be approved. I faxed the comments from the field (page 2 of memo from Stella Yuen dated August 21, 1997) to Mr. Weiss. He indicated that he would respond to the comments by fax as soon as possible.	DATE 8-27-97 ANDA NUMBER 74-712 PRODUCT NAME Lactulose for Oral Solution, 10 g and 20 g packets FIRM NAME - Inalco NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD U.S. Agent Stephen Weiss TELEPHONE NUMBER 212-288-3808 SIGNATURE Karen Bernard, Chemistry Reviewer

Y:\NEW\FIRMSAM\INALCO\TELECONS\74712-T1.WPD

inalco s.p.a.

uffici: via calabiana, 18 - 20139 milano
tel. 02-55213005 r.a. - telefax 02-5694518

telex 332127 inal-i / 324101 inalc-i
telegrammi Inalco Milano
cap. soc. £. 3.000.000.000 delib., £. 2.800.000.000 vers.
registro delle imprese di milano n. 150119
R.E.A. di milano n. 832900
meccanografico MI 032579
c/c postale n. 31404205
codice fiscale 00861350155
partita i.v.a. IT 00861350155

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION
OFFICE OF GENERIC DRUGS
ROCKVILLE, MARYLAND

to the kind attention of: Mrs Karen Bernard
Mrs Stella Yuen

MILANO, September 2nd, 1997 VS. RIF. NS. RIF. mm/97

Ref.: Lactulose (b) (4) **ANDA 74-712**

Dear Sirs,

following FDA comments we have received by your fax dated 27 Aug., here below you can find the limits for all system suitability requirements, as requested.

(b) (4)

From now on, the system suitability will be included in the method of analysis as you can see in the attached methods (double copy).

We hope to have fully satisfied your request, if it was not so or if you needed of any further clarification, please contact us immediately.

Best regards,

Giovanni Cipolletti
Inalco SpA

STEVE WEISS & CO., INC.

September 4, 1997

Fax # 301 443 3839
Ms. Karen Bernard
FDA, CDER, OGD
Rockville, MD

Dear Ms. Bernard:

RE: ANDA 74-712, LACTULOSE (b) (4)
YOUR FAX OF 8/27/97

As agents for Messrs. Inalco, Milan, Italy we are responding to your fax of 8/27/97 concerning system suitability requirements.

Attached are the limits for all system suitability requirements together with the methods of analysis for the (b) (4) and the lactulose crystals.

Thanks for your assistance.

Sincerely,

STEVE WEISS & CO., INC.

L. Stephen Weiss, President

LSW:er
encl

STEVE WEISS & CO., INC.

September 4, 1997

Frank O. Holcombe, Jr., Ph.D
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AM

RE: ANDA 74-712, LACTULOSE (b) (4)

Dear Sir:

As US Agent for Messrs. Inalco SpA, Milan, Italy, the attached fax was sent to Ms. Karen Bernard in response to her fax dated 8/27/97.

Please call if there's additional information needed.

Sincerely,

STEVE WEISS & CO., INC.

Steve Weiss, President
lsw:er
encl (16 + this cover)

CC: Mrs. Kassandra Sherrod, OGD, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855 - 2773

RECEIVED
SEP 5 - 1997
GENERIC DRUGS

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STEVE WEISS & CO., INC

NEW CORRESP

FAX MESSAGE

December 3, 1997

TO: DR. KAREN BERNARD

RE: ANDA # 74-712 LACTULOSE (b) (4)

In response to your December 1, 1997 questions, we submit the following:

1) Particle Size Specifications for the Lactulose Crystals

(b) (4)

We commit to add these to the C of A for all future batches.

2) The specifications ("limits") for Lactose and Galactose have been corrected as per attached table.

Hard copies follow via FedEx in a few days.

Thanks for your cooperation.

Sincerely,

(US Agents for Inalco)

315 EAST 68th STREET● NY, NY 10021● TEL: (212) 288 3808● FAX: (212) 517 3856
e-mail: steveweissco@compuserve.com●visit our website: www.Steveweiss.com

RECORD OF TELEPHONE CONVERSATION

I called Mr. Weiss at the request of the deputy director. I told Mr. Weiss that there were 2 issues that needed addressing. The first was a request for incorporation of a particle size specification for the Lactulose Crystals. The second was a request for clarification regarding a previous amendment dated June 19, 1997. The related compounds limits listed were higher than those proposed by the firm. Mr. Weiss said he would address these 2 issues as soon as possible and respond by fax. I thanked him and gave him my fax number.

DATE 12-1-97

ANDA NUMBER 74-712

PRODUCT NAME
Lactulose for Oral Solution, 10 g and 20 g packets

FIRM NAME - Inalco

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

U.S. Agent
Stephen Weiss

TELEPHONE NUMBER
212-288-3808

SIGNATURE

Karen Bernard, Ph.D.
Chemistry Reviewer

Y:\NEW\FIRMSAM\INALCO\TELECONS\74712.-T2

ANDA/AADA OFFICE LEVEL APPROVAL ROUTING SUMMARY

ANDA # 74-712
AADA #
Drug Lactulose Single Dose packets
Dosage Form Oral Solution
Strength 10g and 20g
Applicant Imtec Sp A
Proposed Action (AP) TA

REVIEWER:

RECEIPT
Date 9/8/97
Initials MS

ACTION
Date 9/12/97
Initials MS

1. Project Manager
Review Support Branch

Original Rec'd date 7/19/95
Date Acceptable for Filing 12/4/95, ~~9/11/97~~
Open Amendment Date(s) 7/30/97
Chemistry Reviewer K Bernard
Supervisor BAmin
Bio Reviewer M. Park
Supervisor R. Mhatre
Date of Office Level Bio Review ~~10/17/97~~
Pending Legal Case Yes ___ No ✓
Comments:

EER Status AC 8/16/97
OAI Status Yes ___ No ✓
Patent Certification ___
Citizen Petition Yes ___ No ✓ If YES attach Email from Project Manager to Petition Coordinator of pending approval

2. Director of Chem. I or II
Office of Generic Drugs
Comments:
10/17/97 - particle size spec to be added to drug substance testing.
12/3/97 - Current amendment OK. Chemistry is satisfactory

Date 9/12/97
Initials

Date 12/3/97
Initials

3. Office Level Chem Review
(1st Generic Only)
Div. Dir. of Chem I or II
Comments:
CMC CONTROLS & SPECIFICATIONS ARE SATISFACTORY

Date ___
Initials ___

Date 12/3/97
Initials

4. P. Rickman
Supv., Reg. Support Branch

Date 12/4/97
Initials

Date 12/4/97
Initials

Contains certification required by the GDEA if sub after 6/1/92
Yes ✓ No ___ //// Determination of involvement? Yes ___ No N/A
Paragraph 4 Certification ___ Yes ✓ No (checklist)
Comments: EES acceptable as 9/8/97, office level Bio OK 10/17/97

5. J. Phillips
Director Division of LPS
Office of Generic Drugs
Comments:

Date 12/4/97
Initials

Date 12/8/97
Initials for J. Phillips

Acceptable EES dated 8/16/97 (printed 12/8/97). No OAI issues noted. Approval based upon suitability petitions (95P-0370/CP1-10g) and (95P-0287/CP1-20g). Bio Waiver granted 3/27/96 (10g) under 320.24(b)(6). FPL Acceptable on 6/2/97 (as endorsed 9/2/97). CMC Acceptable - Chemistry review #5 - on 12/5/97. Methods validation acceptable on 8/21/97. No patent or exclusivity issues. No controlled correspondence pending on this drug product. Bio waiver to extend to 20g package as formulation & process and packaging identical. Recommend: Approve

6. G.Johnston
Deputy Director
Office of Generic Drugs
Patent Cert - P_4 - Yes___ No ✓
Petition status None
Pend. Legal Actions - Yes___ No ✓
Comments:

Date 12/8 Initials JG

Date 12/10/97 Initials JG

Products based on approved suitability petitions
OK to approve

7. D. Sporn
Director
Office of Generic Drugs

J Johnston for

Date_____ Initials_____

Date 12/10/97 Initials_____

R. Williams, MD
1st Generic _____
PD or Clinical for BE_____
Special Scientific or Reg Issues____
Comments:

8. Project Manager K Sherrod

Date 12/10/97 Initials KS

Date 12/10/97 Initials KS

Company Notified
9:55 Time notified of approval via telephone
9:00 Time notified of approval via facismile

LETTER SIGNED: _____
(Name and Date)

(revision date 8-14-96) (X:\wpfile\welsh\rout2.rec)