

LABORATORIES · INC
Braintree

January 14, 1997

Melodi McNeil
Food and Drug Administration
Division of Gastrointestinal Drug Products (HFD-180)
Document Control Room 6B-24
5600 Fishers Lane
Rockville
MD 02180



ORIGINAL

Re: NDA 20-698; 851 (Polyethylene Glycol 3350, NF) Laxative

Dear Ms. McNeil:

With respect to the June 19, 1996 debarment list Braintree Laboratories, Inc. certifies that we did not and will not use in any capacity the services of any person debarred pursuant to sections 305 (a) and (b) of the FD&C Act in connection with the above referenced application.

Please let me know if you need any additional information.

Sincerely,

A handwritten signature in cursive script that reads "Mark vB. Cleveland".

Mark vB. Cleveland, Ph.D.
Vice President
New Product Development

LABORATORIES, INC
Braintree

February 8, 1999

Alice Kacuba
Food and Drug Administration
Division of Gastrointestinal Drug Products (HFD-180)
Document Control Room 6B-24
5600 Fishers Lane
Rockville
MD 20857



NEW CORRESP.

Re: NDA 20-698 MiraLax®; (Polyethylene Glycol 3350, NF Powder)

Dear Ms. Kacuba:

Please be informed that we recently became aware of a patent issued to George Halow claiming a method of use of polyethylene glycol for treating constipation. This method of use is covered by our 505(b)(1) application for MiraLax. This patent has been licensed to Braintree Laboratories, Inc..

In accordance with 21 CFR 314.53(c), the undersigned declares that patent number 5,710,183 covers the formulation, composition and/or method of use of MiraLax. This product is the subject of NDA 20-698 for which approval is being sought. Additional relevant information is as follows:

Effective date: January 20, 1998

Expiration date: January 20, 2018

Please contact me should you have any questions or require additional information.

Sincerely,

Mark Cleveland, Ph.D.
Vice President
New Product Development

ORIGINAL

McNe2

MEMORANDUM

Date: September 17, 1997



SEP 17 1997

To: Lilia Talarico, M.D., Acting Director, Division of Gastrointestinal and Coagulation Drug Product, HFD-180

From: Mohamed Al-Osh, Statistical Reviewer, Division of Biometrics III, HFD-720

Subject: Braintree Laboratories, Inc. Efficacy Results of July 21, 1997 (NDA# 20-698)

Background:

A not- approvable letter, from the Director of the Division of Gastrointestinal and Coagulation Drug Product (G.I.), was sent to the sponsor dated February 24, 1997 on the ground that the analysis of the pivotal Study 851-3 showed no statistically significant difference between PEG 17 or 34gm and placebo. Based on the sponsor's request, a meeting with the sponsor was held on May 8, 1997 to discuss the efficacy results. At the conclusion of that meeting Dr. Talarico recommended that the sponsor conducts a new clinical trial to support their claim of efficacy. However, following a meeting between the sponsor and Murry Lumpkin, M.D., the Deputy Center Director for Review Management, the sponsor submitted on July 21, 1997 the results of their re-analysis for Study 851-3 after changing the definition of constipation to be "less than or equal to 3 BMs per week". The definition of constipation which was used in planning and analysis of the pivotal studies requires "less than 3 BMs per week".

The purpose of this memorandum is to comment on the sponsor's re-analysis of July 21,1997 for Study 851-3 (Attachment I). The comments made here address the sponsor's re-analysis from statistical point of view and disregard of the definition of constipation adapted. The claimed efficacy results presented by the sponsor are misleading and are biased in favor of the drug. There are technical and practical issues related to the sponsor analyses as addressed below:

A. Technical Issues:

- i- Accepting the new definition of constipation for study 851-3, makes the definition of constipation, and consequently the efficacy results, not consistent with those of the second pivotal study (# 851-6).
- ii- Having these analyses done after the primary analysis (which consider less than 3 BMs as a cut-off point in the definition on constipation) one needs to address the new efficacy results as conditional inference. This would require adjusting the alpha level. This reviewer is unaware of simple statistical methods for this adjustment.
- iii- Changing the definition of constipation from that in the original protocol will have consequences on the sample size and the power of the statistical tests. It is not clear how these will have affect on the study findings.
- iv- The sponsor analyzed the data as if the laxative and placebo groups were independent, when in fact the same laxative patients were on placebo during the screening period.

Practical Issues:

- i-The purpose of the placebo treatment during the screening phase was for patients selection into the trial. The purpose was not to create a placebo control. Since some of the patients at the time of their enrollment in the screening period do not meet the definition of constipation, one can not estimate the placebo response rate during the screening period. With this, it is difficult to evaluate the drug efficacy based on the data from the screening period.
- ii- The sponsor statement that the comparison was done against the 'placebo' baseline is misleading and is biased in favor of the drug since placebo itself has a success rate. The '0' rate shown in their placebo group is a result of the elimination of other patients from continuing the study. Thus the claimed 0% placebo rate is a baseline and it does not measure placebo success rate.

The sponsor estimated the placebo response rate in their protocol of Study 851-6, according to the original definition of constipation, as 50% . Thus comparison of the present drug success rate

of 37.5% with '0' merely tests the hypothesis that the drug response rate is different from '0'. But since the placebo success rate itself significantly different from zero, the sponsor's comparison does not support their claim that the laxative response rate is significantly higher than that of placebo..

C. Recommendations:

- i-The sponsor might consider comparing the drug response rate, according to the new definition of constipation (less than or equal to 3 BMs per week) with those of the various placebo response rates during the trial, as done in the Statistical Review, dated July 29, 1996.
- ii- If the claim that the placebo response during the trial is contaminated by the carry-over effect, one might analyze the results of the last seven days of the 10-day treatment period for both the treatment and the placebo responses. Placebo response can not be taken as the baseline measurements (0). Alternatively, Study 851-6 could be viewed as a historical control for the purpose of estimating placebo response.
- iii- Per the sponsor letter of May 1, 1997 (Attachment II), an adjustment in the α -level needs to be made for the interim analysis done in this study, whenever a statistical comparison is made.
- iv. Consistency between the two pivotal studies findings requires that the definition of constipation proposed for Study 851-3 should also be applied for Study 851-6.

Note that these recommendations do not address the technical issues (ii) and (iii) raised above in Section A.

In light of the issues raised in this memorandum concerning the validity of the sponsor's analysis, and in conjunction with previous recommendation made to the sponsor, another clinical trial might still be required to show efficacy. Our comments here, as previously stated, are about appropriateness of the sponsor's analysis from statistical prospective, and disregard of the definition of constipation considered.

/S/ [Redacted]

9/17/97

M. Al-Osh, Ph.D.

Mathematical Statistician

Concur:

Dr. Huque

/S/ [Redacted]

Dr. Smith

/S/ [Redacted]

9/17/97

9/17/97

This memorandum consists of 4 pages of text and 2 attachments.

cc:

Archival NDA 20-698

HFD-103/ Dr. Botstein

HFD-180/ Dr. Talarico/Dr. Canchola/ Dr. Gallo-Torres/Dr. Prizont/Dr. Rubie-Suh/

Ms.McNeil/Ms. Johnson

HFD-720/ Dr. Smith/Dr. Huque/ Dr. Al-Osh

HFD-720/ Chron Copy/ File Copy

APPEARS THIS WAY ON ORIGINAL

LABORATORIES, INC
BrainTree

July, 21 1997



Murry Lumpkin, M.D.
Deputy Center Director for Review Management
Food and Drug Administration (HFD-2)
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-698; 851 (Polyethylene Glycol 3350, NF) Laxative

Dear Dr. Lumpkin:

Thank you for meeting with us to discuss the 851 Laxative NDA. I have attached the analyses for the 851-3 study that you requested at the meeting.

Table 1 shows the efficacy results for a comparison of the first drug treatment period (10 days) to the placebo control period (7 days) for both the 17 and 34 gram doses. As agreed at the meeting, this table was constructed according to the study criteria where constipation was defined as "less than or equal to 3 BMs per week and/or less than or equal to 300 grams of stool per week". Therefore, a successful treatment was defined as "greater than 3BM/week and greater than 300 grams of stool per week". For the 10 day treatment period the success/fail threshold was calculated as 4BMs and 429 grams of stool.

As shown in table 1, comparisons to the control period are highly statistically significant for both doses according to the objective study criteria. In addition, a dose response between the 17 and 34 gram doses in the first treatment period can be demonstrated. The apparently low number of successful responders in the 17 gram dose group is due to two factors: (1) the study population consisted of proven placebo non-responders (placebo responders were eliminated in the control period) and, (2) the study had a 10 day treatment period rather than 14 days used in the later studies. Notwithstanding these caveats, the 37% positive response observed here compares favorably with the estimated 40% non-placebo response noted in the FDA accepted 851-6 study report.

Tables 2 and 3 show both the patient and physician assessments of overall effectiveness for the placebo control and first treatment periods. By this subjective evaluation, 851 treatment was associated with a large improvement in the perception of efficacy. Similarly, patient scoring of bowel movement "ease of passage" and "stool consistency" showed significant improvement during 851 treatment (tables 4 and 5).

Please let me know if you need any additional information. I look forward to hearing from you.

Sincerely,



Mark Cleveland, Ph.D.
Vice President
New Product Development

cc: Paula Botstein, M.D.
Lilia Talarico, M.D.

Table 1
First Treatment Period Responses vs. Placebo Control
851-3 Study Criteria

| | Control | | Treatment | |
|---------|--------------|--------------|---------------|---------------|
| | 17 g | 34 g | 17 g | 34 g |
| Success | 0.0% (0) | 0.0% (0) | 37.5% (9) | 69.2% (18) |
| Fail | 100% (24) | 100% (25) | 62.5% (15) | 30.8% (8) |

Control 17g vs. 17g: $\chi^2 = 11.1$, $p < 0.001$ (Fisher Exact $p < 0.001$)
 Control 34g vs. 34g: $\chi^2 = 27.5$, $p < 0.001$ (Fisher Exact $p < 0.001$)
 17g vs. 34g: $\chi^2 = 5.06$, $p = 0.025$ (Fisher Exact $p = 0.046$)

Success/Fail Criteria

Fail:

Control (7 days): ≤ 3 BMs and/or ≤ 300 g stool
 Treatment (10 days): ≤ 4 BMs and/or ≤ 429 g stool

Success:

Control (7 days): > 3 BMs and > 300 g stool
 Treatment (10 days): > 4 BMs and > 429 g stool

Table 1 compares the first 10 day treatment period responses to 851 laxative to the placebo control period. All patients received placebo during the 7 day control period. The patients were then randomized to a treatment period where they received either a 17 gram daily dose of 851 laxative or a 34 gram daily dose for 10 days. Control period patients that later received 17 grams 851 are shown separately from control period patients that later received 34 grams 851. Treatment success and failure are defined as indicated above according to the study criteria where both stool volume and frequency are taken into account.

Table 2
Patient Assessment
First Treatment Period vs. Placebo Control

| | Control | 17 g |
|------------------|--------------|---------------|
| Success (yes) | 0.0% (0) | 91.3% (21) |
| Fail (no) | 100% (21) | 8.7% (2) |

$\chi^2 = 36.7, p < 0.001$ (Fisher Exact $p < 0.001$)

Table 3
Investigator Assessment
First Treatment Period vs. Placebo Control

| | Control | 17 g |
|------------------|--------------|---------------|
| Success (yes) | 0.0% (0) | 79.2% (19) |
| Fail (no) | 100% (24) | 20.8% (5) |

$\chi^2 = 31.4, p < 0.001$ (Fisher Exact $p < 0.001$)

Tables 2 and 3 show the patient and investigator overall rating of effectiveness for the 7 day placebo control period and the first 10 day treatment period for those patients randomized to 17 gram 851 laxative in the first treatment period. The ratings were made at the end of each treatment period in response to the question "Was the treatment effective?"

Table 2
Patient Assessment
First Treatment Period vs. Placebo Control

| | Control | 17 g |
|------------------|--------------|---------------|
| Success (yes) | 0.0% (0) | 91.3% (21) |
| Fail (no) | 100% (21) | 8.7% (2) |

$\chi^2 = 36.7, p < 0.001$ (Fisher Exact $p < 0.001$)

Table 3
Investigator Assessment
First Treatment Period vs. Placebo Control

| | Control | 17 g |
|------------------|--------------|---------------|
| Success (yes) | 0.0% (0) | 79.2% (19) |
| Fail (no) | 100% (24) | 20.8% (5) |

$\chi^2 = 31.4, p < 0.001$ (Fisher Exact $p < 0.001$)

Tables 2 and 3 show the patient and investigator overall rating of effectiveness for the 7 day placebo control period and the first 10 day treatment period for those patients randomized to 17 gram 851 laxative in the first treatment period. The ratings were made at the end of each treatment period in response to the question "Was the treatment effective?"

Table 4
Patient Scoring of Ease of Stool Passage
First Treatment Period vs. Placebo Control

| Score | Control (n=52) | 17 g (n=117) |
|-----------------------------|-------------------|-----------------|
| 0 (strain) | 32.7% (17) | 8.5% (10) |
| 1 (effort) | 44.2% (23) | 33.3% (39) |
| 2 (easy) | 23.1% (12) | 41.0% (48) |
| 3&4 Urge & no control | 0% (0) | 17.1% (20) |
| Ave. Score | 0.9 | 1.7 |

$r = 0.731$, $SE = 0.027$, $z = 8.56$, $p < 0.001$

Table 4 shows the patient subjective rating of the ease of stool passage associated with each bowel movement for the 7 day placebo control period and the first 10 day treatment period for those patients randomized to the 17 gram 851 dose in the first treatment period.

Patient rating of ease of stool passage was scored on a five point scale of 0 (strain), 1 (some effort), 2 (easy), 3 (urge to go), and 4 (loss of control). A score of 2 would be considered optimal. In the table the percent and the total number of occurrences for each rating is shown. The total number of observations in each category differs because the total number of bowel movements differs between the control and the first treatment period. In the table, the 3 and 4 scores were combined because there was only one bowel movement scored as 4 in the 17g 851 treatment group and none in the control group.

This table was analyzed by ridit analysis (Fleiss, JL, Statistical Methods for Rates and Proportions, Wiley and Sons, NY, NY, 1973) which is discussed in the 851 NDA. Essentially, a ridit (r) is an estimate of the probability that the midpoint of the response to treatment is different from the midpoint of the response of the control group (which is defined as $r = 0.5$).

Table 5
Patient Scoring of Stool Consistency
First Treatment Period vs. Placebo Control

| Score | Control (n=52) | 17 g (n=119) |
|---------------|-------------------|-----------------|
| 0 (hard) | 30.8% (16) | 14.3% (17) |
| 1 (firm) | 28.8% (15) | 16.0% (19) |
| 2 (soft) | 34.6% (18) | 33.6% (40) |
| 3 (loose) | 5.8% (3) | 26.9% (32) |
| 4 (watery) | 0% (0) | 9.2% (11) |
| Ave. Score | 1.1 | 2.0 |

$r = 0.834$, $SE = 0.026$, $z = 12.6$, $p < 0.001$

Table 5 shows the patient subjective rating stool consistency associated with each bowel movement for the 7 day placebo control period and the first 10 day treatment period for those patients randomized to the 17 gram 851 dose in the first treatment period.

Patient rating of stool consistency was scored on a five point scale of 0 (hard), 1 (firm), 2 (soft), 3 (loose), and 4 (watery). A score of 2 would be considered optimal. In the table the percent and the total number of occurrences for each rating is shown. The total number of observations in each category differs because the total number of bowel movements differs between the control and the first treatment period.

This table was analyzed by ridit analysis (Fleiss, JL, Statistical Methods for Rates and Proportions, Wiley and Sons, NY, NY, 1973) which is discussed in the 851 NDA. Essentially, a ridit (r) is an estimate of the probability that the midpoint of the response to treatment is different from the midpoint of the response of the control group (which is defined as $r = 0.5$).

Attachment II

Sponsor's Letter Concerning Interim Analysis

LABORATORIES, INC
Braintree

May 1, 1997

Melodi McNeil
Food and Drug Administration
Division of Gastrointestinal Drug Products (HFD-180)
Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-698; 851 (Polyethylene Glycol 3350, NF) Laxative
"Special Considerations Meeting"

Dear Ms. McNeil:

This letter is to confirm our meeting scheduled for May 8, 1997 from 10 AM until noon in room 6B-45. I have enclosed 8 copies of a proposed meeting agenda.

I have also enclosed bowel movement frequency data requested by the FDA statistician of patients that did not qualify for entry into the 851-3 study. Also, with respect to my pervious statement in the April 23, 1997 supporting documentation submission (page 8) that no interim analysis for the 851-3 study was performed, was in error. An analysis of the first 35 of the 50 enrolled patients was performed prior to completion of the study by the last few patients. I apologize for any inconvenience.

Please call if you have any additional questions.

Sincerely,



Mark vB. Cleveland, Ph.D.
Vice President
New Product Development

interoffice

MEMORANDUM

to: NDA 20-698
from: Eric P. Duffy, Ph.D.
subject: Insert and Immediate Container Labeling
date: December 1, 1998

Refer to Ray Frankewich's review #2 pg 46 for labeling comments. They can be summarized as follows:

1. Clinical reviewer should be made aware of the comments regarding nursing women, and pediatric use.
2. The PRECAUTIONS section indicates [REDACTED]
3. The storage statement on the insert label, and immediate container labels should be revised to [REDACTED]
4. The description section should be revised to change the chemical name for PEG 3350 to be in accord with USP nomenclature.

Additionally - the immediate container labels bear a colored bold MIRALAX which is underlined in colored bold, and beneath this is the established name, Polyethylene Glycol 3350, NF Powder. This is unacceptable - there may not be a line between these two names, as this serves to diminish the prominence of the established name - it should be removed.

/s/ [REDACTED]

Eric P. Duffy, PhD/CMC TL

12/1/98

cc
NDA 20-968
HFD-180/AKacube
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-820/RFrankewich
HFD-820/EDuffy

CSO/Kacuba

NDA 20-698

Braintree Laboratories, Inc.
Attention: Mark vB. Cleveland
60 Columbian Street
P.O. Box 850929
Braintree, MA 02184

JAN 21 1999

Dear Dr. Cleveland:

We acknowledge receipt on December 18, 1998 of your December 17, 1998 resubmission to your new drug application (NDA) for Miralax® (polyethylene glycol 3350, NF) Powder for Oral Solution.

This resubmission contains additional chemistry and labeling information submitted in response to our December 3, 1998 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the user fee goal date is February 18, 1999.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

/s/

1-21-99

Alice Kacuba
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-698
HFD-180/Div. Files
HFD-180/A.Kacuba
DISTRICT OFFICE

Drafted by: A.Kacuba/January 5, 1999
Initialed by: K.Johnson/January 7, 1999
final: AK/January 11, 1999
filename: c:\wpfiles\20698-2nd-CR-1-5-98

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY ON ORIGINAL

Assay:

Stool was analyzed for PEG by a modification of the method of [REDACTED]. Chromium oxide was analyzed by a modification of [REDACTED] 1969 and barium sulfate by a modification of the method of [REDACTED]. The plastic markers were counted following [REDACTED] of the collected stool.

PEG 3350 in Stool: PEG 3350 concentrations in stool was measured by a turbidimetric method. All samples and standards are prepared in triplicate. Stool specimens believed to be free of PEG and these specimens with added PEG, 2.0 g/L, were analyzed. In the assay procedure, 1.00 g of stool was mixed with 1.0 ml of PEG standard (2.0 g/L) instead of 1.0 ml of water. It should be noted that the assay method has a drawback being not specific; it doesn't distinguish PEG 3350 from the lower molecular weight PEGs such as PEG 400, PEG 1000, etc. The validation data provided is not satisfactory. It lacks linearity, sensitivity, accuracy and precision information.

Results:

The results of the analysis of the stool collections for the markers are given below.

Table 1. Percent Total Marker Recoveries

| Subject | PEG | CrO ₄ | BaSO ₄ | [REDACTED] |
|----------------|------------|------------------|-------------------|------------|
| 1 | [REDACTED] | | | |
| 2 ^b | | | | |
| 3 ^b | | | | |
| 4 ^b | | | | |
| 5 | | | | |
| Mean | 65.3 | 75.2 | 55.4 | 78.3 |
| SD | 37.2 | 42.2 | 33.9 | 36.1 |

a Total recovery = 24

b Stools reported lost by patient on interview.

Assay:

Stool was analyzed for PEG by a modification of the method of [REDACTED]. Chromium oxide was analyzed by a modification of [REDACTED] 1969 and barium sulfate by a modification of the method of [REDACTED]. The plastic markers were counted following [REDACTED] of the collected stool.

PEG 3350 in Stool: PEG 3350 concentrations in stool was measured by a turbidimetric method. All samples and standards are prepared in triplicate. Stool specimens believed to be free of PEG and these specimens with added PEG, 2.0 g/L, were analyzed. In the assay procedure, 1.00 g of stool was mixed with 1.0 ml of PEG standard (2.0 g/L) instead of 1.0 ml of water. It should be noted that the assay method has a drawback being not specific; it doesn't distinguish PEG 3350 from the lower molecular weight PEGs such as PEG 400, PEG 1000, etc. The validation data provided is not satisfactory. It lacks linearity, sensitivity, accuracy and precision information.

Results:

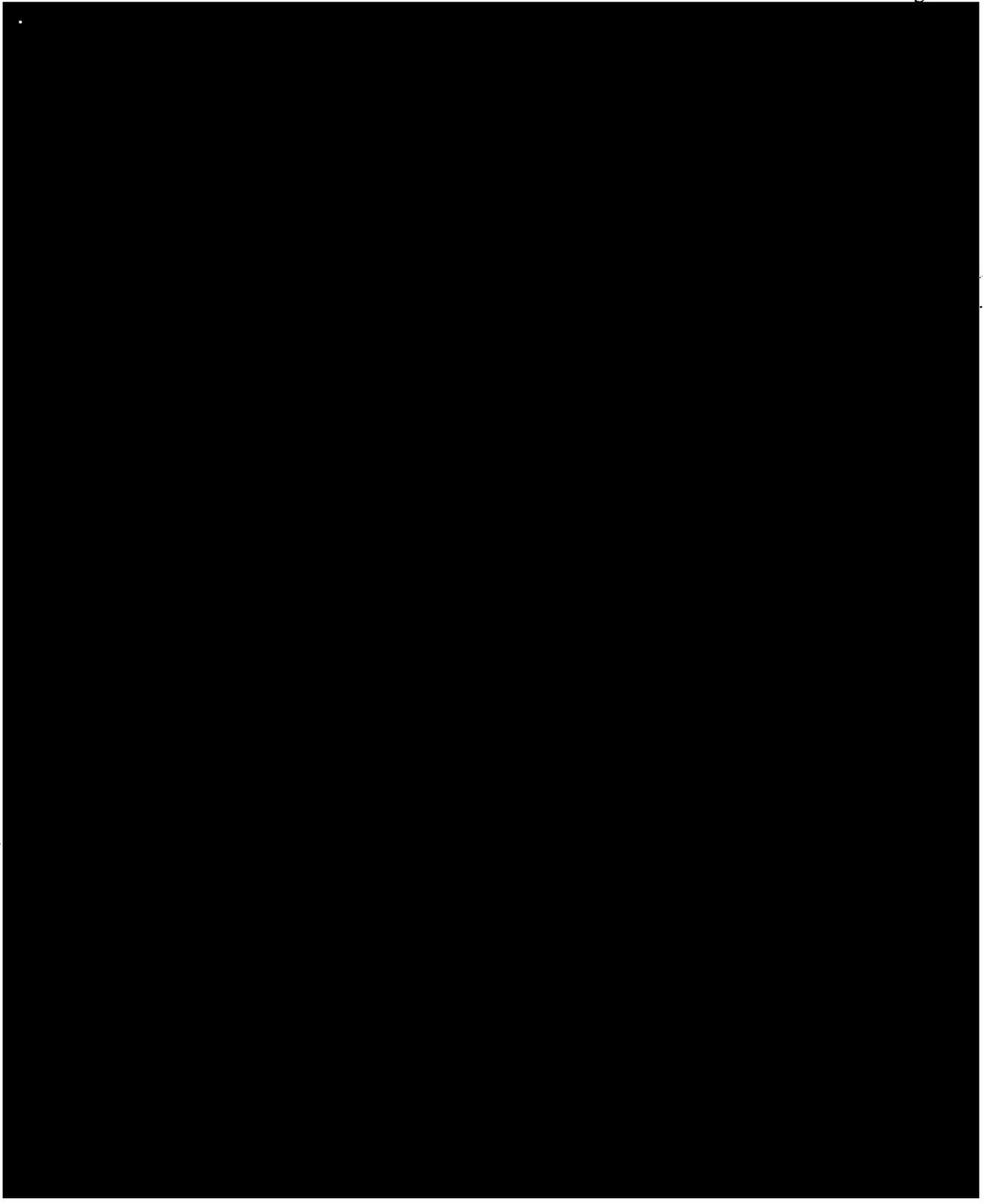
The results of the analysis of the stool collections for the markers are given below.

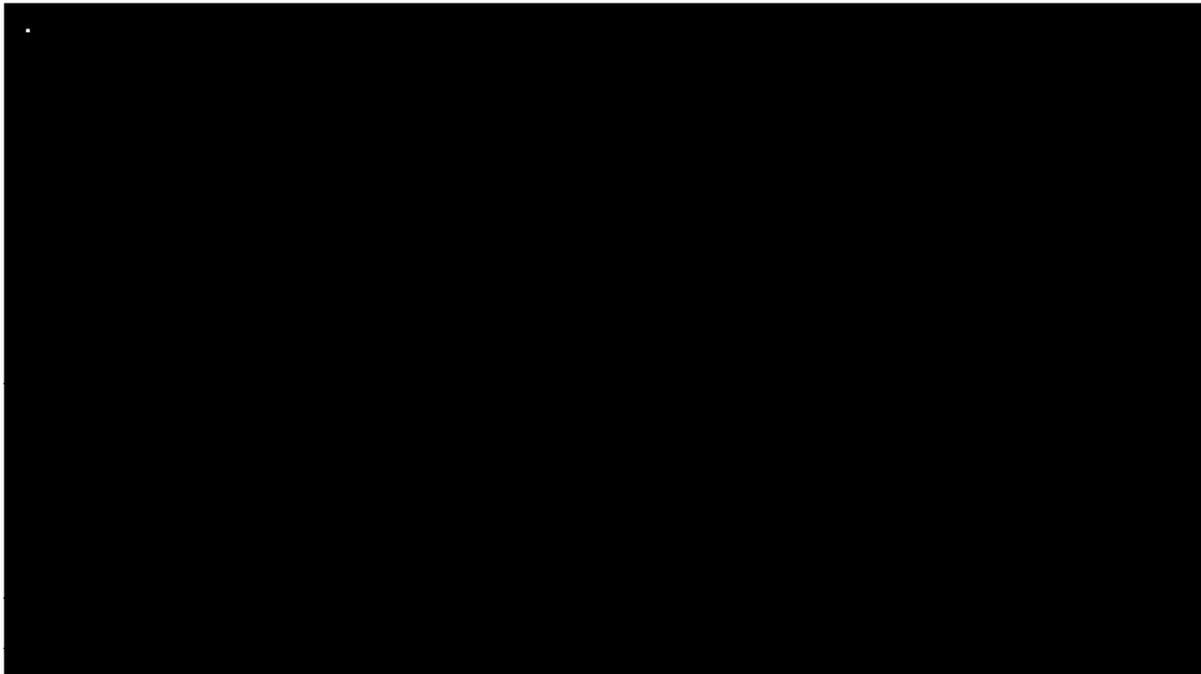
Table 1. Percent Total Marker Recoveries

| Subject | PEG | CrO ₄ | BaSO ₄ | [REDACTED] |
|----------------|------------|------------------|-------------------|------------|
| 1 | [REDACTED] | | | |
| 2 ^b | | | | |
| 3 ^b | | | | |
| 4 ^b | | | | |
| 5 | | | | |
| Mean | 65.3 | 75.2 | 55.4 | 78.3 |
| SD | 37.2 | 42.2 | 33.9 | 36.1 |

a Total recovery = 24

b Stools reported lost by patient on interview.





If you have any questions, contact Alice Kacuba, Consumer Safety Officer, at (301) 827-7310.

Sincerely,

/s/



12/2/98

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug
Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

cc:

Archival NDA 20-698

HFD-180/Div. Files

HFD-180/A.Kacuba

HFD-180/R.Frankewich

HFD-180/E.Duffy

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: A.Kacuba/December 2, 1998

Initialed by: E.Duffy/December 2, 1998

final: A.Kacuba/December 2, 1998

filename: c:\wpfiles\20698812.doc

INFORMATION REQUEST (IR)

APPEARS THIS WAY ON ORIGINAL

Kacuba

NDA 20-698

Braintree Laboratories
Attention: Mark Cleveland
60 Columbian Street West, P.O. Box 850929
Braintree, MA 02185-0929

JUN 23 1998

Dear Mr. Cleveland:

We acknowledge receipt on June 3, 1998 of your June 2, 1998 resubmission your new drug application (NDA) for Miralax[®] (polyethylene glycol 3350, NF) for Oral Solution.

This resubmission contains additional clinical and chemistry, manufacturing and controls (CMC) information submitted in response to our February 24, 1997 action letter.

We consider this a complete, class 2 response to our February 24, 1998 action letter. Therefore, the goal date is December 3, 1998.

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

/s/

6-17-98

Alice Kacuba, RN, MSN
Consumer Safety Officer
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-698
HFD-180/Div. Files
HFD-180/CSO/A.Kacuba
HFD-180/R.Frankewich
DISTRICT OFFICE

Drafted by: AK/ June 12, 1998

Final: AK/06/17/98/c:\mydocuments\NDA20698-06-17-98-ackfullresp

ACKNOWLEDGEMENT (AC)

McNeil

NDA 20-698

Braintree Laboratories, Inc.
Attention: Mark vB. Cleveland, Ph.D.
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185-0929

JUL - 7 1997

Dear Dr. Cleveland:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Miralax (polyethylene glycol 3350, NF) for Oral Solution.

We also refer to the meeting between representatives of your firm and FDA on May 8, 1997. The following represents our summary of the meeting.

Meeting Date: May 8, 1997
Time: 10 AM-12 PM
Location: Rm. 6B-45 (PKLN)

Application: NDA 20-698; Miralax (PEG 3350) Powder for Oral Solution

Type of Meeting: Discussion of 2/24/97 NA letter

Meeting Chair: Dr. Lilia Talarico, Acting Division Director

Meeting Recorder: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

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

- Dr. Lilia Talarico, Acting Division Director
- Dr. Jose Canchola, Medical Officer
- Dr. Hugo Gallo-Torres, Medical Officer
- Dr. Robert Prizont, Reviewing Medical Officer
- Dr. Kathy Robie-Suh, Medical Officer
- Ms. Kati Johnson, Supervisory Consumer Safety Officer
- Ms. Melodi McNeil, Regulatory Health Project Manager

Office of Drug Evaluation III. (HFD-103)

- Dr. Paula Botstein, Acting Office Director

NDA 20-698

Page 2

Division of Biometrics (HFD-720)

Dr. Mohammad Huque, Statistical Team Leader

Dr. Mohammed Al-Osh, Reviewing Statistician

Dr. Abdul Sankoh, Statistician

External Constituent Attendees and titles:

Braintree Laboratories, Inc.

Ms. Vivian Caballero, Director, Regulatory Affairs

Dr. Mark Cleveland, Vice-President, New Product Development

Dr. Jack DiPalma, Investigator

Dr. Wayne Pierson, Statistician

Background: NDA 20-698 was submitted on February 26, 1996 to market Miralax (PEG 3350) Powder for Oral Solution, at a dose of 17 gm, for the treatment of occasional constipation. The firm submitted the following studies in support of approval:

1. 851-3, considered pivotal by the firm, was a single center crossover study which randomized 50 constipated patients to a first period (10 days) of either 17 or 34 gm of PEG therapy. Subsequently, without a washout interval, subjects were randomized to second or third periods of placebo (PBO) or the alternate PEG dose.
2. 851-4 was a nursing home study identical in design to Study 851-3. Four of the first five patients treated with either 17 or 34 gm of PEG experienced diarrhea. Subsequently, the PEG doses were reduced to 6 and 12 gm for the remaining 30 patients.
3. 851-5 was a single-center crossover study in which 25 patients were randomized to PEG 17 gm or PBO.
4. 851-6, considered pivotal by the firm, was a parallel study which enrolled 151 subjects who were randomized to PBO or PEG 17 gm.

In a February 24, 1997 Not Approvable letter the firm was informed that while Study 851-6 provided support for the 17 gm dose of PEG, though only after 7 days of treatment, Study 851-3 was insufficient to support approval. The letter stated that an additional robust, adequate and well-controlled study would be necessary to demonstrate efficacy of the 17 gm dose. Further, in light of the diarrhea experienced by the elderly subjects enrolled on 17 or 34 gm of PEG in Study 851-4, the firm was requested to provide additional safety data on the proposed dose so that the drug's risks could be adequately characterized. On March 26, 1997 Braintree Laboratories, Inc. requested a meeting with the Agency to discuss the clinical deficiencies in the

NDA 20-698

Page 3

Not Approvable letter. Prior to today's meeting, the firm requested and received the clinical and statistical reviews of the application.

Meeting Objectives:

1. To discuss the differences of opinion that exist with regard to the efficacy demonstrated in pivotal Study 851-3.
2. To obtain Agency feedback on the design of a future clinical trial.

Discussion Points:

1. Discussion of Study 851-3:

According to the firm, after a 7 day placebo control period, 50 patients qualified for this study according to the prospectively defined inclusion criteria of ≤ 3 bowel movements and/or ≤ 300 gm of stool per week. In response to questions, the firm acknowledged that, although not specified in the protocol, no patient received PBO in the first treatment period, based on a belief that subjects would not tolerate a long period of time (7 days of placebo run-in + 10 days of the first treatment period, 17 days total) without active treatment. The firm also acknowledged that some patients were enrolled, at the discretion of the investigator, who did not meet the inclusion criteria.

Dr. Cleveland expressed the firm's position that the best way to assess Miralax's efficacy is to determine how many patients ended the study non-constipated, according to the protocol. The firm analyzed the last 7 days of each treatment period in an attempt to minimize any carryover effects as a result of the crossover design and set a significance level of $p=0.05$. Dr. Cleveland said all design issues were resolved at a November 5, 1987 meeting with the Agency, however, no written documentation of that meeting is available. Ms. Johnson offered that the firm was informed of the Division's serious reservations with the adequacy of this study at the August 20, 1990 meeting.

Based on the 39 patients in each group with complete data, Dr. Cleveland indicated that PBO versus PEG 17 gm was significant for stool weight but not for stool frequency. It was the firm's position that, since the results were positive according to the protocol, the study should be considered in support of the compound's efficacy.

Agency representatives expressed the following concerns:

NDA 20-698

Page 4

- Dr. Prizont noted that, according to the protocol for the study, patients were to be randomized to 1 of the 3 treatments in the first period. However, although patients received all 3 treatments over the course of the trial, no subject received PBO in the first treatment period, therefore, period 1 was not randomized as prospectively established.
- Dr. Huque observed that the data set was did not reflect an all patient analysis, nor did it use a full crossover design analysis model. He questioned the firm's use of the least significant difference (LSD) test for analysis and said Dunnett's test may be more appropriate. Further, he advised the firm to make sure results were not analysis-dependent.
- The study's inclusion criteria of ≤ 3 bowel movements and/or ≤ 300 gm of stool per week does not correlate with the definition of constipation the Agency has historically preferred (from the Federal Register tentative OTC laxative monograph): < 3 bowel movements per week. The firm was informed at the March 9, 1994 meeting with the Agency that this would be the criteria upon which the Agency would evaluate efficacy.
- The firm did not appear to have performed the reanalyses, requested in the August 20, 1990 meeting, of "relief" or "no relief" of constipation as a binary endpoint, defined according to the Federal Register. The firm was also advised at this meeting to relate a proportional improvement on a per patient basis or demonstrate a response in the most severely constipated subset of patients, then look for a historical control of this group.
- The clinical relevance of stool weight as an endpoint was questioned.

In response, the firm indicated that they had performed a subgroup analysis of the most constipated patients as requested, although it was not presented in the NDA, nor was a historical control provided. It was their position that, of patients who had ≤ 2 bowel movements per week during the PBO control period, 61% completed the study with their constipation relieved.

In response to a question from Dr. Robie-Suh, Dr. Cleveland said, according to the protocol, patients who "completed" the study may not have finished each

NDA 20-698

Page 5

treatment group; patients who experienced diarrhea during a treatment period were allowed to skip the remainder of that period and proceed to the next period, as long as they completed at least 5 (of 10 total) days in the period. Dr. Prizont noted that 17 patients discontinued one phase of Study 851-3 because of diarrhea, and Dr. Robie-Suh commented that, as designed, the protocol allows patients who experience diarrhea to contribute to the measure of efficacy, since they are counted as a success.

According to the firm, Miralax does not exert a profound effect until after approximately 6 days of treatment, although there is a trend towards efficacy from the beginning of therapy. Dr. Cleveland questioned the Agency's method of statistical analysis, which concentrated on the first 7 days of each treatment period, saying that it did not represent a reasonable evaluation of the compound's efficacy. Dr. Talarico noted the firm's use of the word "occasional" in the proposed indication and said that word implied a more rapid onset of action than 6 days. Further, she noted that the firm's draft labeling contained the following statement in the DOSAGE AND ADMINISTRATION section: "Twenty four to forty eight hours may be required to produce a bowel movement." In response, Dr. Cleveland clarified that this statement reflects the trend towards efficacy seen at the beginning of therapy with Miralax and stated that the firm was willing to revise the labeling to more accurately state when a laxative effect could be expected.

Dr. Al-Osh questioned whether the firm had performed the reanalysis in terms of success/failure, as requested at the August 1990 meeting. Dr. Cleveland responded that the protocol was not designed for that type of analysis and said the study was contaminated for an endpoint imposed after its implementation. Dr. Cleveland reiterated the firm's position that Study 851-3 in combination with Study 851-6 provided evidence of safety and effectiveness to support approval of Miralax 17 gm. Dr. Talarico responded that, as presented in the NDA, efficacy results were inconsistent, much of the analyses were retrospectively applied, and there did not appear to be two adequate and well-controlled studies as required by the regulations. In addition, Agency representatives commented that as early as 1990, the firm was advised that it was questionable as to whether a complete analysis of this study could be performed, given its execution.

A number of analyses were presented in today's meeting that were not in the NDA. The firm was informed that these analyses could be submitted to the Agency as part of their full response to the Not Approvable letter.

Dr. Botstein reminded the firm that the Agency considered Study 851-6 as

NDA 20-698

Page 6

supportive of approval and offered the following advice on the design of another study to replicate it.

2. Proposed Study

- **DESIGN**

The firm was advised to conduct an additional randomized, double-blind, placebo-controlled, parallel study with a 14 day treatment period.

- **ENDPOINTS**

Agency representatives suggested a binary endpoint (responders versus non-responders, where "responders" are defined as those who go from constipated [less than 3 bowel movements per week] to non-constipated).

- **ANALYSIS**

The firm was asked to analyze the first 7 days of the study, then the entire 14 days. They were also requested to prospectively address how they will manage missing data, if any. Dr. Talarico said any interim analyses should be rigorously defined in advance in terms of frequency and timing, in addition to statistical correction. The Agency recommended that any interim analysis be done by an independent third party.

- **PLACEBO**

Although this is a parallel study, the placebo should be designed such that it closely matches the active drug in, among other things, taste.

- **STUDY POPULATION**

If the firm wishes to include dosing information in the elderly, safety and efficacy must be shown in that population. This could be satisfied through a sub-group analysis, provided there was sufficient enrollment.

The firm was advised to submit the protocol, request Agency feedback, and wait for a response before initiating the study.

3. Dr. Botstein indicated that if the results of a new study are positive and provide replication of Study 851-6, there are still unresolved issues regarding Miralax's

NDA 20-698
Page 7

safety in elderly patients and labeling for the general population. Dr. Cleveland said . . .



4. Several Agency representatives questioned the firm as to exactly what patient population this drug was intended to treat, given that it takes nearly a week to show effect. Further, they noted the apparent contradiction between the firm's earlier statement that investigators in 851-3 did not believe patients could wait a long time before treatment with active therapy and their current claim that patients would be willing to wait almost a week for a response, especially given the wide variety of over-the-counter treatment options available for constipation. In response, the firm indicated that they plan for Miralax to be used in the treatment of short-term constipation episodes in patients who are chronically constipated, although Dr. Cleveland added that Miralax is not intended for chronic use.
5. The firm was reminded that the labeling must provide useful information for health care professionals about all aspects of the compound's use. Among other things, it should specify how long the drug is to be used and the patient population for which it is indicated.

Summary:

1. Approval of Miralax will be based on evidence of safety and efficacy from at least two adequate and well controlled studies. As presented in the NDA, Study 851-3 is insufficient to support approval.
2. The firm was advised to conduct an additional adequate and well controlled study, to be used in combination with Study 851-6, in support of approval. The firm was also given suggestions as to the design of this study and requested to submit the protocol for Agency comment prior to initiation.
3. As an alternative, the firm was informed that they could reanalyze Study 851-3 and submit that reanalysis as their response to the clinical deficiencies in the Not Approvable letter.
4. As specified in the Not Approvable letter, additional safety information in elderly patients is necessary before the drug can be approved, since they comprise a significant proportion of the potential users.

NDA 20-698

Page 8

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager,
at (301) 443-0483.

Sincerely yours,

/s/

7-7-97

/s/

7/7/97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-698
HFD-180/Div. Files
HFD-180/CSO/M.McNeil

Drafted by: mm/July 7, 1997/c:\wpfiles\cso\n\20698707.min
final: July 7, 1997

GENERAL CORRESPONDENCE (MINUTES SENT)

APPEARS THIS WAY ON ORIGINAL