McNeil

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER REVIEW

NDA: 20-698 DEC 26 1996

Sponsor: Braintree Laboratories, Inc.

Drug: "851" PEG 3350 Laxative, powder form

Indication: Treatment of Occasional Constipation

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Date Received by DGCDP: March 1, 1996

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Medical Officer: Dr. Robert Prizont, MD

Documents Reviewed: Submitted Braintree Volumes 1, 2 , 3 , 4
IND [redacted]
Dr. Kathy Robie-Suh, DGCDP Medical Officer, Reviews of IND [redacted]
Dr. M. Al-Osh, FDA Statistician Reviewer, Reviews of July 29, 1996, September 9, 1996 and December 2, 1996.
Federal Register, March 25, 1975 and January 15, 1985

APPEARS THIS WAY ON ORIGINAL

A. INTRODUCTION AND BACKGROUND.

## A. INTRODUCTION AND BACKGROUND.

1. Brief Review of Previous Applications and Basic PEG Properties and Pharmacology; Taken from Braintree Vol. 1, Present Submission, Sections of Pages 4 through 56.

*"Polyethylene Glycol 3350 is an accepted excipient for drug use (National Formulary XV Page 1244) and is an accepted food additive recognized in Title 21. Extensive toxicologic and pathologic studies on this component are included in Union Carbide Corporation Drug Master File".*

Braintree states that according to performed *in vitro* studies, PEG 3350 is not metabolized by the intestinal flora (Page 51).

851 Laxative is composed of Polyethylene Glycol 3350, NF (PEG 3350). *"PEG 3350 is the major osmotic component of Braintree Laboratories' PEG-Electrolyte Lavage Solutions (GolYTELY® or PEG-ELS and NuLYTELY® or SF-ELS) approved as NDAs 19-011 and 19-797".*

*Both PEG-ELS and SF-ELS were developed using a total gut perfusion method to measure water and electrolyte absorption during lavage in normal volunteers. Both PEG-ELS and SF-ELS contain PEG 3350 as the dominant osmotic agent. A single dose of SF-ELS contains 420 grams of PEG 3350 and a single dose of PEG-ELS contains 230 grams. The results of these studies showed net absorption or secretion of water and electrolytes with PEG-ELS or SF-ELS.*

Subsequent to these studies, Braintree carried out Protocol 851-2a. Braintree states that Protocol 851-2a was designed *"to evaluate the effects of reduced doses on stool volume and electrolyte excretion. Four doses of NuLYTELY were evaluated in a blinded, randomized, cross-over protocol. Five consecutive female adult subjects were enrolled and all subjects enrolled completed the study protocol". The sponsor notes that "Each treatment period was followed by a seven day wash out period and then the next seven day treatment period was began with another dose, etc". The four daily doses evaluated contained "1/8, 1/16, 1/32 and 1/64 of the PEG and electrolytes of the 4 liters SF-ELS (NuLYTELY)".* ***These doses are equivalent to 52 g, 26 g, 13 g and 6 g of PEG 3350, respectively. The results of this 851-2a study were displayed by Braintree in the following Table 8, Page 53, Vol. 1.***

**Table 8**
**Weekly Wet Stool Output (grams) and BM Frequency**
**Laxative Effects of Low Dose SF-ELS**
**(Braintree Protocol #851-2a)**

| | | Daily SF-ELS Dose | | | |
|---|---|---|---|---|---|
| | Control | 1/64 | 1/32 | 1/16 | 1/8 |
| Total Stool Output (grams per 7 days) | 166.9 | 269.0 | 415.1 | 560.5 | 578.4 |
| BM Frequency | 1.8 | 2.8 | 4.4 | 5.4 | |

In the discussion of the table, Braintree states that ***"a large, significant increase in both BM frequency and total stool output was evident as the dose of SF-ELS was increased"***. Braintree then added that ***"As indicated in the table the most appropriate dose seems to be in the range of 1/32 to 1/16 the single bolus dose for lavage (equivalent to 13 to 26 grams PEG)"***.

Braintree conducted two additional studies using 17 g or 34 g of PEG 851. These studies, conducted under protocols Braintree 851-2b and Braintree 851-2c, were designed to assess the recovery of orally administered PEG-851 in stools of constipated patients. In each of these studies 5 constipated patients were given a PEG dose for 1 or 2 days, alone or together with a non-absorbable marker such as chromium oxide. After a few days, these constipated patients were given a strong laxative [redacted] or a mannitol lavage to evacuate their bowels. According to the sponsor, collection of evacuated stools was very difficult , i.e., several stool specimens were lost. In spite of this technical difficulty, Braintree states it was able to determine that most of the orally administered PEG remains in the intestinal milieu as non-absorbed PEG, and that a very small amount of the administered dose, e.g. <1%, is absorbed, and either lingers in the extracellular space for short periods or is rapidly eliminated in the urine.

On Page 58, Vol. 1, Braintree concludes the following: ***"The 851-2b study and Hammer et al (Hammer HF et al. Studies of osmotic diarrhea induced in normal subjects by ingestion of polyethylene glycol and lactulose. J Clin Inv., 84:1056-1062, 1989) demonstrate the laxative effects of small doses of NuLYTELY. This effect is attributed to polyethylene glycol 3350, the dominant osmotic component. The 851-2b study also indicates that an appropriate dose would contain about 17 grams PEG 3350 per day. Both studies show that no electrolytes should be added to the laxative formulation as they appear to be absorbed"***.

## B. DRAFT DRUG LABEL.

Pages 1 and 3, Vol. 1. in ***Indications and Usage***, and in ***Dosage Administration***, the draft label states the following:

DRAFT LABELING

[redacted]

DRAFT LABELING

[redacted]

**C. 45 Day Filing of NDA 20-698.**

[redacted]

**D. SUPPORTIVE CLINICAL DATA.**

In support of the proposed label claim, Braintree submitted the efficacy results of two pivotal trials, Protocol 851-3 and Protocol 851-6.

***1. Pivotal Studies.***

***Protocol Study 851-3.*** Vols. 1 and 2.

***I. Study Protocol.***

- The submitted Protocol for Braintree Study 851-3. Vol. 2, has two parts. Part I, Pages 1-17 consists of ***Informational Material*** on Phase I and II studies and the drug labeling identification for investigators. Part II includes the ***Study Plan***. The following is a brief descriptive summary of the Study Plan. Only relevant sections are mentioned in this summary,

  a. *Note from Reviewer.* On Page 19 of the ***Outline of Planned Investigations***, this 851-3 Protocol states that it was prospectively designed as two *"studies"*. The protocol states that one *"study"* will have Dr. Reichelderfer as principal investigator and Dr. Hamilton as co-investigator (University of Wisconsin-Madison) and *"will be conducted with constipated outpatients"*. The other study will be have Dr. DiPalma as principal investigator (University of South Alabama); *"this study will be conducted with constipated inpatients"*. Apparently, the DiPalma study was subsequently not carried out or was discontinued. Thus, I will only refer to the study plan designed for Dr. Reichelderfer.

  b. *Number of Patients and Duration of Study.* The protocol instructs for approximately 50 subjects enrollment (no statistical planning or prospective rationale for sample size was provided). The protocol states that each subject will spent 40 days in the study.

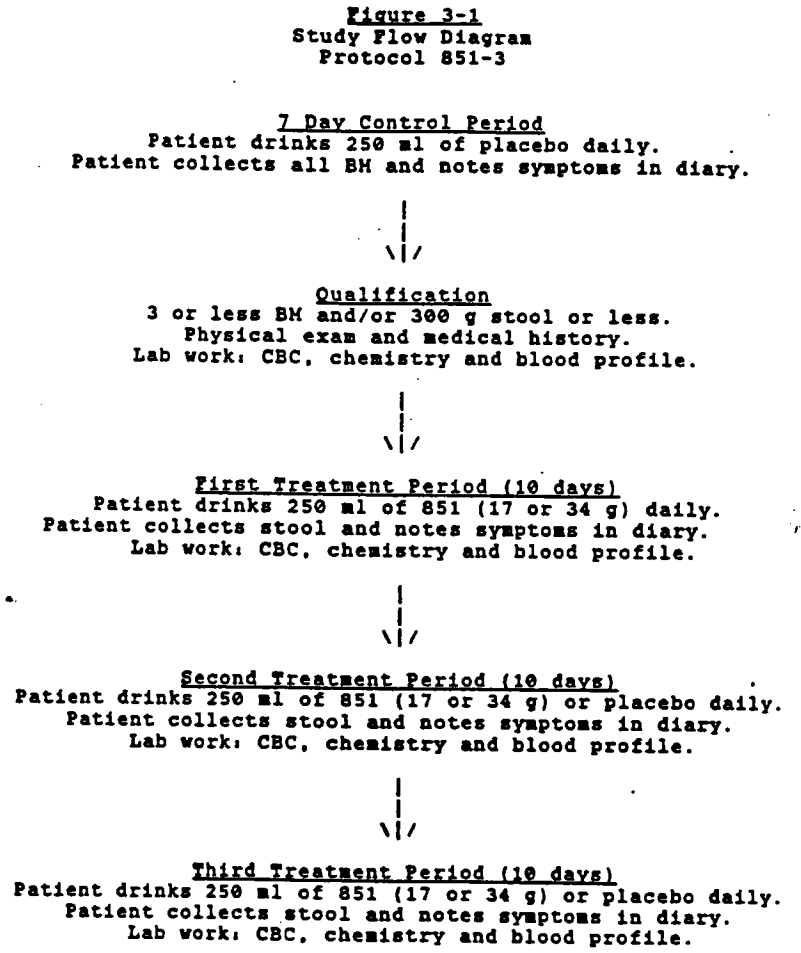
  c. *Inclusion and Exclusion Criteria.* Volunteer "men or women of legal age " ; ***"after one week run in period volunteers must meet criteria for constipation". This protocol defines constipation as "less or equal to three bowel movements per week and/or less than or equal of 300 grams of stool per week".*** Excluded will be persons weighing less than 100 lb (45.45 Kg), persons having gastrointestinal obstruction and pregnant women or women who *"expect to become pregnant during study"*.

  d. *Drugs and Doses.* PEG 851 17 grams, PEG 851 34 grams and Placebo.

  e. *Study Design.* Crossover, double-blind, placebo control design. The prospective protocol calls for **constipated patients** to be **selected** during **a placebo run-in**, ***"seven day control period".*** **After the placebo run-in** period, selected constipated ***"subjects will be randomized to receive one of three treatments: placebo, 17 grams PEG, or 34 grams PEG (in 250 cc of flavored water)".*** For the ***next ten days, each subject will drink the appropriate randomized treatment. "After the first 10 days, the subjects will be crossed over to an alternative treatment according to the randomization schedule.***

*After the second 10 days is completed, the patients will again be crossed over to the final randomized treatment".* During each period, subjects will collect stools and record the frequency of bowel movements and consistency of stools during passage.

**Braintree Study Flow Diagram for Protocol 851-3 is shown below** (copied and pasted from **Page 3-10, Vol. 2**).




f. *Data Analysis.* The protocol states that ***"Only the data from the last seven days of the 851 treatment will be analyzed . Efficacy will be demonstrated by comparing the bowel movement frequency and stool output resulting from each dose of laxative use to that from the control (placebo) period".***

***ii. Descriptive of Study 851-3.***

- The following is this reviewer summary of the relevant issues included in the Braintree descriptive of study 851-3. This single center study was conducted at the University of Wisconsin-Madison by Dr. Reichelderfer between April 1988 and January 1990. *Braintree's description of study 851-3 included* the following sections: *Introduction, Investigational Plan and Efficacy* Results (Pages 3-4 to 3-40, Vol. 2), This *reviewer will summarize the descriptive in* the following sections: *Subject Population and Demographics, Treatment Order in Crossover Periods, Patient Disposition and Efficacy Results.*

*a. Subject Population and Demographics.* Braintree states that 50 consenting adults were enrolled. According to Braintree, ***"all 50 subjects enrolled completed the study"***. The enrollment encompassed 3 male and 47 female subjects; *"one enrolled patient was black and the rest were of Caucasian origin"*. Patients ages ranged from 19 to 69 years of age with an average of 36.2 years.

*b. Treatment Order in Crossover Periods.* ***"Following a seven day control period which patients were given placebo, qualified patients were randomized to a three treatment schedule where they received one of the three possible treatments (34 gram dose, 17 gram dose or placebo) in each 10 day treatment period. Placebo was not given in the first treatment period"***. Braintree included the **Patient Randomization for Study 851-3 in Table 3.2, Page 3-11, Vol. 2.**

***Braintree's Patient Randomization Table 3.2, created for Study 851-3, is included in this review as Appendix 2.***

On Page 3-77, Braintree shows an *"order"* of the crossover schedule displayed in columns from Braintree computerized efficacy tables. The *"order"* indicates the ***"order of drug administration a given patient was assigned. Each sequence was assigned a number as follows (P indicates placebo):***

***1 = 17g, P, 34g***
***2 = 17g, 34g, P***
***3 = 34g, P, 17g***
***4 = 34g, 17g, P "***.

Regarding the **absence of a placebo** arm in the first randomized drug treatment, Braintree explains on Page 3-12, Vol. 2, the following: ***"This was because it was the investigators***

***clinical experience that constipated subjects would be unwilling or unable to complete a 10 day placebo treatment following a seven day control period ( where no laxative was given) without a significant bowel movement. Indeed, it was initially believed that study subjects would be unable to tolerate a placebo treatment at all. This was discussed at a meeting between FDA and Braintree on 11/5/87 which resulted in the protocol submitted 11/23/87";*** Braintree refers the reader to Appendix 3-C, Vol. 2. In Appendix 3-C, there is a letter from Braintree to the FDA consumer safety officer in which Braintree states the new protocol for study 851-3 will include a placebo arm in the second and third 10 day periods. Included in this Appendix 3-Care also minutes from a August 20, 1990 meeting between the HFD-180 Division Director and Braintree, with comments from the Division Director about the design of study 851-3. I was unable to find any minutes of the November 5, 1987 meeting referred by the sponsor. Similar comments on the absence of this November 5, 1987 meeting are found in the medical officer review of [redacted]

***The Letter and Minutes submitted by Braintree in Appendix 3-C, Pages 3-208 to 3-211, are included as Appendix 3 of this review.***

*c. Patient Disposition.* In **Table 3.22, Page 3-48, Vol. 2**, Braintree shows the *"subjects not included in the final analysis"*; Braintree **Table 3.22 is shown below.**

Table 3.22
Subjects not Included
Protocol 851-3

| Patient Number | Reason |
|---|---|
| 89 | Pre-enrollment patient developed flu during control period. This patient was later evaluated and enrolled into the study as patient 50. |
| 7 | Enrolled patient was dropped from the study due to non-compliance with protocol and never received study drug. |

On Page 3-77, Vol. 2, Braintree states that ***"17 patients discontinued one phase of therapy due to diarrhea. These were 14, 20, 22, 41 and 43 during the 17 gram dose***

***treatment and patients 3, 14, 16, 10, 23, 29, 30, 32, 39, 41, 42 and 51 during the 34 gram dose treatment. Patient 21 discontinued therapy during the placebo treatment phase due to lack of efficacy. Patient 27 complained of rectal irritation during placebo treatment and discontinued the medication".***

*d. Efficacy Results.*

*1. Primary Efficacy. Stool Weight and Stool Frequency.* Braintre states that ***"The primary efficacy variables (stool weight and frequency), analyzed by repeated measures ANOVA, are given in tables 3.4 and 3.5", taken from Page 3-21, Vol. 2.***

Table 3.4
Mean Daily Wet Stool Output (grams)
(Braintree Protocol #851-3)

| | Placebo | 17 grams | 34 grams |
|---|---|---|---|
| Mean | 41.0 | 58.4 | 84.7 |
| SEM | 6.05 | 7.13 | 9.8 |

p < 0.001 DF=2,72 F=76.7
(SEM = standard error of mean)

Table 3.5
Mean Daily Bowel Movement Frequency
(Braintree Protocol #851-3)

| | Placebo | 17 grams | 34 grams |
|---|---|---|---|
| Mean | 0.45 | 0.54 | 0.82 |
| SEM | 0.04 | 0.05 | 0.09 |

→ p < 0.001 DF=2,76 F=10.8
(SEM = standard error of mean)

Braintree explains that ***"These tables show the mean daily stool output and mean daily bowel movement frequency for each 10 day treatment period. Highly statistically significant responses were evident for stool output and bowel movement frequency as the dose of 851 laxative was increased from placebo. For both stool weight and frequency, the response to the 17 gram dose was not significantly different from the response to placebo but the response to the 34 gram dose was significantly different from the response to the 17 gram dose or placebo (p<0.05). This provides clear***

***evidence of laxative efficacy for 851 laxative.***
*Braintree tables 3.6 and 3.7 show the results of* ***mean daily dry stool weight and mean daily stool water content resulting from each 10 day treatment period. These tables demonstrate that much of the observed increase in stool weight was attributable to an increase in water content., consistent with the hypothesized osmotic effect of PEG 3350.***

***For or both stool dry weight and water weight, the response to the 17 gram dose was significantly from the response to placebo ($p<0.05$) and the response to the 34 gram dose was significantly different from the response to the 17 gram dose or placebo ($p<0.05$)".***

2. *"Cross-Over Effects"*. Braintree states (Page 3-24, Vol. 2) that possible cross-over effects were analyzed to comply with the FDA request stated in the meeting of August 20, 1990 (see Appendix 3, this review). According to Braintree, the cross-over effects may occur ***"when placebo treatment follows high dose laxative treatment and a laxative effect is carried over into the placebo period".***

As shown in the section ***b,*** *Treatment Order and Crossover Periods,* there were four possible orders of treatment (see section *b* in this present review descriptive of study 851-3). **In the following Table 3.8, Page 3-25, Vol. 2, Braintree** presented the possible effects on stool weight of the crossing-over from one experimental treatment into the next experimental treatment.

**Table 3.8**
**Mean Daily Stool Weight**
**Analysis of Cross-Over Effect**
**(Braintree Protocol 851-3)**

| | Treatment Order | | | | | | |
|---|---|---|---|---|---|---|---|
| Treatment | 17,P,34 | 17,34,P | 34,P,17 | 34,17,P | F | DF | p |
| Placebo ($\bar{X}$) | 32.4 | 25.5 | 57.3 | 37.2 | 2.60 | 3,45 | 0.06 |
| SEM | 5.5 | 6.1 | 12.7 | 6.4 | | | |
| n | 9 | 14 | 14 | 12 | | | |
| 17 g ($\bar{X}$) | 53.8 | 42.1 | 69.8 | 66.8 | 1.26 | 3,44 | 0.3 |
| SEM | 11.5 | 8.6 | 13.8 | 14.4 | | | |
| n | 8 | 15 | 14 | 11 | | | |
| 34 g ($\bar{X}$) | 84.2 | 69.3 | 97.7 | 96.1 | 0.44 | 3,36 | 0.73 |
| SEM | 16.6 | 17.1 | 20.9 | 24.9 | | | |
| n | 7 | 11 | 12 | 10 | | | |

SEM = Standard Error of Mean

***received the 34 gram dose and 23 received the 17 gram dose"***. In the following **Table 3.10, Page 3-29, Vol. 2**, Braintree illustrates the mean daily stool weight from patients administered during the first period, either the 34 gram or 17 gram PEG 851 dose

Table 3.10
Mean Daily Wet Stool Output (grams)
First Treatment Period
(Braintree Protocol #851-3)

| | 17 grams | 34 grams |
|---|---|---|
| Mean | 46.6 | 88.7 |
| SEM | 6.55 | 14.1 |

p = 0.01 DF=1,44 t=2.71
(SEM = standard error of mean)

During this **first treatment** period, ***"daily stool output was significantly different between the two doses with a nearly two-fold increase for the 34 gram dose as compared to the 17 gram dose"***. As comparison, Braintree provided the mean stool weight in the **control pre-treatment** period; it was 30 grams for patients randomized to the 17 g PEG dose and 29 g for subjects randomized to the 34 g PEG dose. Braintree notes that this similar daily stool weight during the pre-treatment control period, demonstrates that *"the two groups were equivalent at baseline"*.

In this first treatment period, *"a statistically significant difference in bowel movement frequency between the two doses was also observed. This is shown below in Table 3.11"*. In the control pre-treatment period. daily bowel movement frequency was similar for patients randomized to the first period; i.e., 0.31/day for 17 g PEG recipients and 0.32/day for 34 g PEG recipients. The following table is Braintree **Table 3.11**, cut and pasted from **Page 3-30, Vol. 2**.

Table 3.11
Mean Daily Bowel Movement Frequency
First Treatment Period
(Braintree Protocol #851-3)

| | 17 grams | 34 grams |
|---|---|---|
| Mean | 0.52 | 0.80 |
| SEM | 0.05 | 0.09 |

p = 0.05 DF=1,45 t=2.07
(SEM = standard error of mean)

As regards to the mean daily stool weight, Braintree concluded that ***"There were no statistically significant crossover effects from any of the treatment orders for any of these therapies"***. Braintree added that ***"Although not statistically significant, the 34g, P, 17 g treatment order seem to result in more stool output for placebo treatment than any of the other orders. Crossover analysis for stool water content does indeed yield a statistically significant result (p=0.04) for placebo in the 34g, P, 17g order"***.

In the next **Braintree Table 3.9, Page 3-27, Vol. 2**, the sponsor shows the possible impact of crossing over therapies on stool frequency.

Table 3.9
Mean Daily Frequency
Analysis of Cross-Over Effect
(Braintree Protocol 851-3)

| | Treatment Order | | | | | | |
|---|---|---|---|---|---|---|---|
| Treatment | 17,P,34 | 17,34,P | 34,P,17 | 34,17,P | F | DF | p |
| Placebo ($\bar{X}$) | 0.33 | 0.40 | 0.63 | 0.36 | 5.44 | 3,45 | 0.003 |
| SEM | 0.17 | 0.06 | 0.06 | 0.05 | | | |
| n | 9 | 14 | 14 | 12 | | | |
| 17 g ($\bar{X}$) | 0.51 | 0.52 | 0.72 | 0.53 | 1.47 | 3,43 | 0.23 |
| SEM | 0.09 | 0.06 | 0.08 | 0.12 | | | |
| n | 8 | 15 | 13 | 11 | | | |
| 34 g ($\bar{X}$) | 0.85 | 0.73 | 0.69 | 0.90 | 0.31 | 3,38 | 0.82 |
| SEM | 0.26 | 0.14 | 0.08 | 0.24 | | | |
| n | 7 | 11 | 12 | 10 | | | |

SEM = Standard Error of Mean

Braintree concluded that ***"No crossover effects were observed for bowel movement frequency except for placebo following the 34 gram dose in the 34g, P, 17g treatment order. A crossover effect from laxative treatment to placebo treatment would only tend to obscure the true efficacy of the laxative (by inflating the placebo response)"***.

*3. First Treatment Period Comparison.* Braintree reports that ***"In the first 10 day treatment period*** *following the seven day control (enrollment) period* ***22 study subjects***

Braintree concludes that ***"The data presented in Tables 3.10 and 3.11 demonstrates a dose dependent response to 851 laxative and clear evidence of efficacy in the first treatment period as required by FDA"*** (see Memorandum of Meeting, Appendix 3 of this review).

**iii. Reviewer Comments.**

***1. Views on Constipation.*** Perhaps the best example of the difficulty general internists, clinical gastroenterologists and investigators encounter in defining constipation is summarized in the introduction on definition of constipation in the rather recent edition of Bockus Gastroenterology, Chapter 4, Page 102, Vol. 1, 1995. The author, Dr. Timothy Koch, Associate Professor of Medicine, Medical College of Wisconsin states the following: *"Many physicians consider the problem of constipation trivial, yet it is one of the most common digestive disorders.* ***One of the major problems in dealing with chronic constipation is defining it.....In different people, constipation may represent infrequent defecation or straining with defecation, passage of firm or small volume fecal material,*** *pain with defecation, or a discrepancy between expected output and actual results with regard to bowel habits and stool consistency".*

Customarily, the medical literature uses frequency of bowel movements per week, e.g., less than 3 bowel movements per week, to define constipation. This usage originated in a large study conducted around the greater London area in the 1960's. This survey 1055 healthy factory workers and 400consecutive patients without gastrointestinal disease. (Connell AM et al. Variation in bowel habit in two population samples. BMJ, 2:1095-1099, 1965). This agency refers to this definition in section C of Federal Register, Proposed Establishment of Monographs for OTC Laxative, Vol. 40, Page 12904, 1975, and in *comments 44,* OTC Laxative *Tentative* Final Monograph, Federal Register, Vol. 50, Page 2133, 1985 (in this comment, the agency defines constipation as *"no more than three evacuations per week"*). ***It should be noted, however, that this agency does not have yet a firm and well established definition of constipation, because the final monograph version has not been concluded.*** For instance, in other sections of the same OTC Laxative *Tentative* Final Monograph, Page 2127, the agency accepts the use of *"irregularity"* as synonymous of constipation, as taken from the Webster's New Collegiate Dictionary, Springfield, MA, 1979, and, in the Proposed Establishment of Monographs for OTC Laxative, the agency also defines constipation as *"infrequent, or difficult evacuation of the feces"*, taken from Dorland's Illustrated Medical Dictionary, Saunders Co. 1965.

Stool weight has been examined as a possible objective measure. However, there appears to be a wide range of stool weight between individuals, e.g., 35 g to 225 g

daily. In normal individuals, stool weight is definitely influenced by the amount of fiber in the diet (Muller-Lisner S. Effect of wheat bran on weight of stool and gastrointestinal transit time; a meta analysis. Br. Med. J., 296:615-617, 1988). Depending on the use of the word constipation, e.g., hard stools, there is a difference in prevalence between gender and with age. Women have been reported to complain of constipation 2-3 times more often than men (Heaton KW et al. Defecation frequency and timing and stool form in the general population: A prospective study, Gut, 33:818-824,, 1992).

*2. Validation of Results.* The results presented by Braintree in Tables 3.4 and 3.5 shows seeming overall success in the relief of constipation in patients administered the 34 g PEG 851 dose. The same Braintree overall results revealed lack of efficacy in the relief of constipation after the administration of the 17 g PEG 851 dose; **17 g is the PEG dose proposed by Braintree in its submitted draft drug label (see Section B. DRAFT DRUG LABEL, this review)**. The overall primary efficacy results presented by Braintree in this 851-3 study, one of two pivotal trials, revealed that those patients randomized to receive a 17 g dose of PEG 851 for a period of 10 days, had significantly fewer bowel movements and less stool output than patients administered twice a dose of PEG, 34 g. Further, and according to these Braintree results, the mean frequency of bowel movements or stool output in constipated subjects administered PEG 17g, was not statistically different from the mean stool frequency and mean stool output of patients receiving a placebo flavored water.

The validity and accuracy of the overall 851-3 efficacy results presented by Braintree are in doubt, because of the incompleteness of the submitted information and inconsistencies in the presented data. Namely, these deficiencies are the following:

> *(a) Concerns on Populations Analyzed.* As noted in the review of the statistician reviewer, the sponsor did not report the patient population included in the efficacy analysis presented in Tables 3.4 and 3.5 (see statistician review, Page 5, July 28, 1996). Thus, it is unclear whether these Braintree analyses were calculated using an all intention-to-treat patient population, or using completed patients or by including only those patients who on a per-protocol basis were considered by Braintree as evaluable
>
> The correct number of patients used in the calculation of the Braintree efficacy results are of relevance for, as reported by Braintree, there was a marked imbalance in the number of patients who had to be discontinued from a particular randomized experimental treatment due to the development of diarrhea (see Descriptive of study 851-3, section *c. Patient Disposition*, this review). The following MO Reviewer Table 1 exemplifies this point.

MO Reviewer Table 1

Study 851-3. Patients Discontinued on Treatment Due to Diarrhea

| Patient Population | Number * |
|---|---|
| Total Discontinued On Treatment | 17 (100%) |
| Discontinued While on 34g PEG | 12 (71%) |
| Discontinued While on 17g PEG | 5 (29%) |
| Discontinued While on Placebo | 0 (0%) |

* Taken from information provided by Braintree in Page 3-77, Vil. 2

*(b) Consistency of Submitted Results.* The primary efficacy results for study 851-3, presented by Braintree in Tables 3.4 and 3.5m Page 3-21, Vol. 2, were also shown by Braintree in **Table 3.1, Page 3-5, Vol. 2.** *As seen in the following Braintree Table 3.1, the results appear not to be entirely consistent with the results shown by Braintree in Tables 3.4 and 3.5. For instance, in Table 3.5, Braintree reports a mean frequency of bowel movements (BM) for patients on 34 g PEG of 0.82/day. In the following Braintree Table 3.1, the frequency of BM for patients on 34 g PEG is 0.73/day.*

**Table 3.1**
**Daily Wet Stool Output (grams) and BM Frequency**
**(Braintree Protocol #851-3)**

| | Placebo | 17 grams | 34 grams |
|---|---|---|---|
| Stool Output (daily grams) | 41.9 | 59.8 | 87.8 |
| BM Frequency (daily) | 0.46 | 0.54 | 0.73 |

$p < 0.001$

*(c) Need for Washout Period.* The crossover design of this 851-3 study did not include a washout interval after the first treatment period with PEG, in which the 50 patients were exposed for 10 days to either 17 g PEG or 34 g PEG. The carry-over drug effect from the exposure to PEG was evident in patients placed

on placebo subsequent to the 34 g PEG treatment. *The sponsor illustrated the cross-over effect in Braintree Tables 3.8 and 3.9* (see *section 2. "Cross-Over Effects"*, Descriptive of 851-3, this review).

The sponsor did not provide any analysis to ascertain the *drug-effect* between the 17 g and 34 g PEG. In order to bypass a possible carry-over drug-effect between the two PEG doses, the statistician reviewer calculated the primary efficacy using the data from the first treatment period. The following is statistician reviewer Table 12, copied from Page 22 (Dr. M, Al Osh review).

Table 12/ Reviewer's Analysis, Study 851-3
Comparison of the mean bowel movements and % of success
for the 1st treatment

| Treatment | N.Pat | Mean(SE) | p-value[1] | % success [3] | p-value[2] |
|---|---|---|---|---|---|
| i)10 days treatment, all patients | | | | | |
| 1st trt 17g | 24 | 5.000 (0.442) | | 67% (16/24) | |
| placebo | 24 | 3.625 (0.407) | 0.023 | 46% (11/24) | 0.146 (0.245) |
| 1st trt 34g | 26 | 6.846 (0.828) | | 73%(19/26) | |
| placebo | 26 | 5.038 (0.495) | 0.067 | 73%(19/26) | 1.00 (0.755) |
| ii)10 days treatment, excluding patients base ≥ 3 | | | | | |
| 1st trt 17g, | 15 | 4.267 (0.358) | | 53%(8/15) | |
| placebo | 15 | 3.067 (0.317) | 0.018 | 33%(5/15) | 0.269(.462) |
| 1st trt 34g, | 16 | 6.187 (0.963) | | 63%(10/16) | |
| placebo | 16 | 4.125 (0.515) | 0.069 | 63%(10/16) | 1.00(.715) |

[1] p- value is based on the t-test
[2] p- value is based on $\chi^2$( Fisher's Exact)test
[3] For the 10-treatment success is taken as ≥ 4 b.m.

*i. Observations.* The data shown in the statistician reviewer Table 12 shows that the mean daily bowel movements in patients on the 17 g dose was significantly higher than that of placebo. It also reveals a lack of significance in the difference between mean daily bowel movements in patients on 34 g PEG dose and patients on placebo. These results from the statistician reviewer are in contrast from those submitted by Braintree and underlines the importance of a careful analysis of any carry-over drug-effect caused by the particular cross-over design used in this trial.

*(d) Interim Analysis.* The Braintree protocol for study 851-3 did not prospectively planned for an interim analysis of the data. The *Investigational Plan* submitted by Braintree, in Volume 2 (1.4.2) of this NDA, states there was a plan for interim data analysis but that no actual interim analysis was performed (Page 3-8).

***Page 3-8, Vol. 2, Braintree Investigational Plan is included as Appendix 4 of this review.***

My research of IND [redacted] revealed that Braintree did conduct an interim analysis. This interim analysis was conducted after enrollment of 35 (70%) of the total 50 patients prospectively planned (this single center study actually enrolled 50 subjects). The efficacy data of this interim analysis was submitted to the Director of DGCDP as part of a Braintree pre-NDA outline, and was received by DGCDP on March 5, 1990. The primary efficacy data obtained from this interim analysis revealed that patients administered the 34 g of PEG for 1 week became non-constipated, as illustrated by a mean frequency of bowel movements above 3/week and a stool output > 300 g/week. On the other hand, patients administered the 17 g PEG for 7 days continued to meet the protocol's definition of constipated, and were only slightly improved from placebo patients. **Braintree's interim analysis Table 1, taken from Page 11 of the aforementioned pre-NDA outline is shown below.**

Table 1
Madison Interim Analysis (n=35)
(mean ± SD)

| Measure | Placebo | 17 grams | 34 grams | p |
|---|---|---|---|---|
| Wet Stool Weight (g) (per 7 days) | 213.4 (161.9) | 355.1 (221.8) | 488.0 (343.2) | <0.01 |
| Frequency (BM per 7 days) | 2.94 (1.85) | 4.74 (2.31) | 5.66 (3.80) | <0.01 |

*I. Observations.* Conducting an unplanned interim analysis of primary efficacy with 30% of the prospectively planned patient population needed to be enrolled, commonly requires adjustment of the p-Value with possible decrease in the statistical significance of results (as discussed with the statistician reviewer, Dr. M Al Osh). It appears unlikely that p-Value adjustment for a single interim analysis would change the statistical significance shown in reviewer Table 12 (see previous page). It is also unclear whether this interim analysis, not reported in this NDA submission, was the only interim analysis conducted by the sponsor.

*(e) Protocol Violations.* **A total of 13/50 (26%) of subjects randomized to the study, had not met the protocol definition of constipation**, i.e., ≤ 3 bowel movements/wk or ≤300 g stools/wk in the run-in period, as seen in this next MO Reviewer Table 2.

MO Reviewer Table 3

Study 851-3 Inclusion Criteria Violations of Protocol's Definition of Constipation

| Patient Number | Mean Stool Frequency and Stool Output In Qualifying Seven Day Run-In Period * | | Order Patients Were Randomized After Run-In Period |
|---|---|---|---|
| | Stool Frequency bm/week | Stool Output g/week | |
| 8 | 3 | ***325*** | 34g-17g-Pl |
| 13 | 2 | ***399*** | 17g-Pl-34g |
| 14 | 3 | ***344*** | 17g-Pl-34g |
| 19 | 3 | ***464*** | 34g-Pl-17g |
| 21 | 3 | ***344*** | 17g-Pl-34g |
| 25 | 3 | ***424*** | 34g-Pl-17g |
| 28 | 2 | ***370*** | 34g-Pl-17g |
| 29 | 3 | ***442*** | 17g-34g-Pl |
| 34 | ***4*** | 253 | 34g-17g-Pl |
| 36 | ***4*** | 192 | 17g-34g-Pl |
| 40 | 3 | ***309*** | 17g-Pl-34g |
| 45 | 3 | ***614*** | 34g-Pl-17g |
| 46 | 3 | ***486*** | 17g-Pl-34g |

* According to the study protocol, patients had to have ≤3 bowel movements per week (bm/week), and ≤300g of stool per week (g/week), to qualify for the study. Numbers highlighted in bold-italic font are those patients who were enrolled without meeting the definition of constipation prospectively established in the study protocol.

***3.*** *Handling Constipation Endpoints.* As noticed in Table 12 (see subsection 1-c, comments section), the statistician reviewer expressed the efficacy results as mean frequency of bowel movements as well as proportion of success or failures in each treatment group. The first comparison represents the actual *quantitative* mean of stools in a 10 day period. The second comparison is a *qualitative binary representation of constipated or non-constipated subjects*. The statistician performed this latter analysis to comply with the recommendations from the DGCDP Division Director stated in the meeting with Braintree on August 20, 1990 (see Page 3, Appendix 3, this review).

The results of the *quantitative analysis of mean stool frequency show a significantly higher mean stool frequency in patients first administered PEG 17 g than in those crossed over to placebo treatment.* Further examination of the data also shows that after the placebo treatment, placebo patients were no longer meeting the definition of constipation established in the study protocol, i.e., mean bm in placebo patients was 3.63 bm/week. In this sense, placebo was also effective in the relief of constipation.

The binary comparison of efficacy simply attempts to establish the proportion of patients who, after experimental therapy, no longer met the definition of constipation. This comparison perhaps appears more realistic, in view of the difficulties reported by Braintree in assessing with some sort of accuracy the number of stools and/or the stool output in outpatients during a 10 day period. This difficulty in assessing the exact number of stools has been reported in the gastroenterological literature (Ashraf W et al. An examination of the reliability of reported stool frequency in the diagnosis of idiopathic constipation. A. J. of Gastroent. 91:26-32, 1996). *As illustrated in the statistician Table 12*, the *binary comparison of successes, showed no significant difference in the relief of constipation between the PEG doses and placebo treatment.* It should be noted that the statistician reviewer calculated the rate of success or failure by applying a definition of constipation distinct from the established in the study protocol. As recall, the 851-3 study protocol required a stool frequency of more than 3 bowel movements a week to be considered as no longer constipated. The footnote in the statistician Table 12 states that *"for the 10 (day)-treatment success is taken (defined) as ≥ 4 bowel movements".* Thus, **subjects who had more than 2 bowel movements per week were considered by the statistician reviewer no longer constipated and entered as therapy success in the efficacy rate estimate.**

APPEARS THIS WAY ON ORIGINAL

*Study 851-6.* Vol. 3 and IND [redacted]

*I. Study Protocol.*

- *a. Note from the Reviewer.* Braintree submitted several protocols for study 851-6. **I found a protocol for study 851-6 in** [redacted] **This protocol was apparently the original prospective protocol submitted in April 2, 1991. This prospective protocol was again submitted to the DSI in early 1994 together with data from an interim analysis.** This submission included a cover letter dated January 27, 1994 from the Braintree Vice President of New Product Development (Dr. M Cleveland), to Dr. Bette Barton, DSI/FDA. In his letter, Dr. Cleveland states that **this study was originally designed as a single center study (Dr. DiPalma) with enrollment by this center of 200 patients.** Because of the low enrollment in Dr. DiPalma site, three other centers were added, each responsible for enrolling 50 patients. At the time of this letter, the study was still ongoing.

***The January 27, 1994 letter from Dr. Cleveland to Dr. Barton, IND*** [redacted] ***is included as Appendix 5 of this review.***

**A second amended protocol was drafted after the interim analysis of efficacy had been completed (>70% of patients had been already enrolled). This amended protocol was included in the Annual Report submitted to the IND in March 13, 1996 and was included in this NDA submission (Braintree states that amending of the protocol took place as a result of a meeting with the DGCDP on March 9, 1994 and was submitted to the DGCDP on May 12, 1994). This amended protocol has a listing of all participating centers and an amended data analysis section as well as an amended enrollment of 150 patients..** Unless otherwise noted, I will describe the relevant issues included in the prospective protocol submitted in IND 28,306.

*b. Study Centers.* Originally the only site was the GI Division at the University of South Alabama (Dr. J A DiPalma). During the trial the following centers were added: Gastrointestinal Specialists, PC (Dr. P DeRidder), GI Division, University of Florida College of Medicine (Dr. B Koltz), GI Section, Tulane University Medical Center (Dr. R Orlando). The protocol states that each investigator may enroll up to 50 patients.

*c. Study Design. **This section of the protocol states the following: "This study will be a double blind parallel design study, conducted with volunteer outpatients. Subjects will be unaware as to whether the treatment is active or placebo (dextrose)". "Patients will be selected during a seven day control period where they will keep a diary of bowel habits recording frequency of bowel movements, etc".*** After the one week run-in period, ***"volunteers must meet criteria for constipation (2 or less bowel movements per week). Qualified subjects will be randomized to receive either active drug (PEG 17 grams) or placebo for a fourteen day period".***

*d. Duration of the Study. "21 days per subject. One year for the study".*

*e. Inclusion Criteria.* Volunteers men or women 18 or older who after the one week run-in period, meet the criteria of constipation (see point c of this protocol's description).

*f. Exclusions. "Persons weighing less than 80 lb. persons having a history of gastrointestinal obstruction or other organic cause of constipation, gastric retention, gastric perforation, toxic colitis, megacolon, bowel resection, colostomy, women of child bearing potential not using effective contraception".*

*g. Efficacy.* ***The protocol states that "Treatment efficacy will be defined as those patients who no longer meet the definition of constipation during the treatment period (i.e., 3 or more bowel movements per 7 days in the treatment period)". "An ineffective treatment (treatment failure) is defined as less than 3 BM per week".*** *"If the subject has no bowel movement during the treatment period and a laxative is administered (other than the test drugs), they will be considered to have failed the treatment. Similarly,* ***if a subject experiences continuing diarrhea, defined as more than three large watery stools per day (i.e., patient subjective evaluation of abnormally large, watery bowel movements), during the treatment period this will also be considered a treatment failure (as well as an adverse reaction). In both cases, the treatment will be discontinued and the patient removed from the study".***

*h. Data Analysis.* The **original protocol states** that ***"Efficacy analysis will include an intent-to-treat analysis which will include all patients randomized into the double blind treatment period*** *as well as an* ***evaluable analysis which will include only those patients who completed the entire study. Study subjects who experience diarrhea or who used a non-study laxative during the study will be considered treatment failures".***

The **amended protocol states** that *"The efficacy evaluation will include an intent-to-treat analysis which will consider all patients randomized into* ***an initiating the first and second week of the double-blind treatment period. An evaluable analysis*** *will also be done which* ***will include only those subjects who completed or contributed enough data to categorize as to success or failure during the first or second week of the treatment period. Study subjects that use a non-study laxative during the study will be considered treatment failures".***

Both protocol versions state that an interim analysis will be performed after 50 patients of each treatment group have completed the treatment.

***ii. Descriptive of Study 851-6.***

*a. Duration.* This study lasted 3 years and 4 months, from August 1991 to December 1994 (Page 6-1, Vol. 3, or Braintree 1.4.3).; it was titled ***"17 grams Dose of 851 Laxative versus placebo. A Blinded, Randomized, Parallel Trial Multi-Center"***.

*b. Patient Population.* [In the original submission ,Braintree stated that subsequent to the selection of constipated patients during the one week run-in control period, **151 adult subjects were randomized into two groups** (according to a randomization order shown as Table 6.2a, Page 6-11, Vol. 3). Braintree then states that ***"Efficacy analysis was based upon 144 patients"***. **Seven patients were excluded,** 4 apparently for non-compliance (patients *6*, 133, 308 and 309). Patients 207 and 217 were withdrawn by the investigator because of abnormal baseline labs. Braintree continues the explanation on excluded patients by noting that ***"patient 144 was a re-enrollment of patient 114"***. Braintree then notes that ***"patient 6 was included in the overall patient and investigator efficacy ratings since the data was available"***. In reference of those patients who finished the two study periods, Braintree states that ***"135 of the study subjects fully completed the protocol"***].

- Subsequent to the original submission but before the 60 day filing deadline, Braintree amended parts of the above version. In this new version, Braintree states that ***"Efficacy analysis was based upon 147 patients. Four patients were excluded, patient 133 (for non-compliance); patient 144 (a re-enrollment of patient 114); patients 207 and 217 were withdrawn by the investigator following abnormal baseline labs".*** Also, Braintree now states that ***"131 patients fully completed the protocol"***.

*c. Demographics.* Braintree reported age, sex and race in the population demographics (race was included only for 3 of the 4 enlisted centers). Centers 2 and 4 had a predominance of whites, 84% and 70% whites vs 16% and 30% blacks, respectively. In contrast, center 3 enrolled similar proportion of whites and blacks, 53% whites and 47% blacks. As regards to sex distribution, 131 female and 20 male subjects were enrolled in this 851-6 study. Braintree reports that the average age was 45 years (43.4 y to 49.1 y).

*d. Further Braintree Explanations on Data Analysis. They are the following:*

(1) On Page 6-19, Vol. 3 or Braintree 1.4.3, Braintree states that ***"For efficacy criteria, calculated p values of $p \leq 0.04$ were considered significant. The value of $p \leq 0.04$ was selected to account for an interim analysis performed when enrollment had reached 100 patients"***.

(2) Subsequent to the NDA submission, Braintree informed the FDA team coordinator that in ***"the evaluable analysis, only patients completing at least 3 days of the first treatment week were considered (Page 6-18)***".

(3) On page 6-22, Braintree explains that assessment of patient efficacy was based on success or failure per each week (≥3 BM per week). Thus, **to assess patient efficacy in the 2 week period**, each completed patient ***"received two scores, one for each week of treatment"***.

*e. Efficacy Results.*

*1. Intent-To-Treat.* Braintree notes that ***"In this analysis a patient completing one day would be scored as a treatment failure unless they had three bowel movements during that day. A patient that withdrew after the first week was considered a treatment failure for both weeks. A total of 147 patients were thus evaluated for both week 1 and 2 out of 151 enrolled. This adds 7 patients over the evaluable analysis"***.

Braintree states that ***"the second week of treatment showed the greatest differential response between the two treatments. This analysis is presented in tables 6.7-6.9 below and demonstrates clear evidence of 851 laxative efficacy"***. Braintree **Tables 6.7-6.8-6.9, Page 6-27, Vol. 3,** is shown below.

**Table 6.7**
**Treatment Success for Both Weeks**
**Intent-To-Treat**
**(Braintree Protocol 851-6)**

| | Success | Fail |
|---|---|---|
| %851 (n) | 65.8% (104) | 34.2% (54) |
| %Placebo (n) | 47.8% (65) | 52.2% (71) |

$p < 0.005$, $X_2 = 9.72$, $n = 294$

**Table 6.8**
**Treatment Success for Week 1**
**Intent-To-Treat**
**(Braintree Protocol 851-6)**

| | Success | Fail |
|---|---|---|
| %851 (n) | 63.3% (50) | 36.7% (29) |
| %Placebo (n) | 50% (34) | 50% (34) |

$p > 0.05$, $X_2 = 2.64$, $n = 147$

**Table 6.9**
**Treatment Success for Week 2**
**Intent-To-Treat**
**(Braintree Protocol 851-6)**

| | Success | Fail |
|---|---|---|
| %851 (n) | 68.3% (54) | 31.6% (25) |
| %Placebo (n) | 45.6% (31) | 54.4% (37) |

$p < 0.005$, $X_2 = 7.77$, $n = 147$

*2. Evaluable.* Braintree included 140 patients for the evaluable analysis of week 1 and 135 for the evaluable analysis of week 2. The following Braintree **Table 6.5, Page 6-24, Vol. 3**, reveals the results of the "evaluable data" for the week 1 of treatment. Braintree states that ***"during the first week of treatment the proportion of success and failures in the 851 laxative group was statistically different from that in the placebo group. About 68 percent of patients that received 851 had a 'successful' response to the therapy while (as expected) 50 percent of the placebo recipients had a 'successful' response. This provides clear evidence of 851 efficacy".***

Table 6.5
Treatment Success for Week 1
Evaluable Data
(Braintree Protocol 851-6)

| | Success | Fail |
|---|---|---|
| %851 (n) | 68.5% (50) | 31.5% (23) |
| %Placebo (n) | 50.7% (34) | 49.3% (33) |

$p < 0.04$, $X^2 = 4.59$, $n = 140$

Braintree showed the evaluable analysis for the week 2 of treatment, in the following **Table 6.6, Page 6-25, Vol. 3**. Braintree comments that ***"Of those 135 patients providing evaluable data for the second week of treatment, there was a highly statistically significant difference between treatment groups. 76% of 851 recipients (or 52% of presumed placebo non-responders) showed a clear laxative effect and were no longer constipated according to the definition".***

Table 6.6
Treatment Success for Week 2
Evaluable Data
(Braintree Protocol 851-6)

| | Success | Fail |
|---|---|---|
| %851 (n) | 76.1% (54) | 23.9% (17) |
| %Placebo (n) | 48.4% (31) | 51.6% (33) |

$p < 0.001$, $X^2 = 11.01$, $n = 135$

In the following **Table 6.17, Page 6-36, Vol. 3**, Braintree shows the Treatment Success by

Center, in Braintree's intent-to-treat population. Braintree states that in this table, ***"the total number of treatment successes and the total number of treatment failures is given for each treatment week as well as for both treatment weeks combined. In the table, a patient that completes the first treatment week is counted once (as a success or a failure). The same patient is then counted again for the second treatment week"***. Braintree notes that the table shows no statistically significant differences in the proportions of treatment success and failures among the study centers.

**Table 6.17**
**Treatment Success by Center**
**Intent-To-Treat**
**(Braintree Protocol 851-6)**

| Center | Week 1 S/F | Week 2 S/F | Total S/F |
|---|---|---|---|
| 1 | 27/19 | 26/20 | 53/39 |
| 2 | 26/22 | 28/20 | 54/42 |
| 3 | 19/11 | 20/10 | 39/21 |
| 4 | 12/11 | 11/12 | 23/23 |
| $X^2$ | 0.92 | 1.94 | 2.50 |
| P | 0.82 | 0.58 | 0.48 |

S = Success, F = Failure

**iii. Reviewer Comments.**

*1. Efficacy.*

*(a) The Week 1 Presented Data. According to the intent-to-treat data of successes and failures, as presented by Braintree in Table 6.8, Study 851-6 (see subsection e. Efficacy Results, this review), 1he* ***administration to a group of constipated subjects (79) of a 17 g/day dose of PEG-851 solution for a period of one initial week, was not significantly superior than the administration of a placebo solution given to another group of constipated subjects (68) during the similar initial one week*** *treatment period.* The data of this first week treatment does show a numerical trend, i.e., 13%, favorable to the PEG 851 laxative therapy.

As stated in the protocol, for the purposes of this study, treatment success is defined as the passage of three bowel movements in a period of one week.

*(b) The Week 2 Presented Data.* The ***sponsor's intent-to-treat data for the second week of treatment***, Table 6.9, Study 851-6, *(see same subsection e.)* ***reveals a significantly higher rate of success with the PEG 851 laxative.*** According to the data presented by Braintree, there was a 22% efficacy difference favorable to the 851 laxative.

*© The Week 1+2 Presented Data.* The final efficacy results for both weeks

combined, as presented by the sponsor, is not acceptable. As noticeable in Braintree Table 6.7 the sponsor is not examining the overall final two week study results for 147 subjects, but rather, of 294 subjects. This is so, for in its estimate, Braintree counted each event/week and each patient/week, and then added events plus patients for the two weeks of treatment (as observed in Braintree Table 6.17, see descriptive). Doubling the number of events and number of patients would spuriously turn significant any numerical superiority of the 851 laxative, or transform into highly significant, any otherwise borderline significant result.

*(d) Adjustment of Statistical Significance.* As stated in my *Descriptive* section, Braintree decided to adjust the final significance of efficacy results for this study 851-6 to a p-Value ≤0.04 (two sided). According to Braintree, this post-study adjustment in the significance of final results takes into account the interim look on efficacy performed during the trial. ***Braintree stated that this interim analysis was carried out after 50 patients on each treatment had completed the protocol.***

In his review, the FDA statistician reviewer argues that this adjustment does not take into consideration the following: *(1) Braintree terminated the trial after assessing the efficacy results of 151 patients enrolled in the trial, despite the fact that the protocol prospectively established a final enrollment of 200 constipated subjects; (2) To the statistician request of information on number of interim analyses, Braintree submitted, on May 9, 1996, results on an interim analysis conducted on 119 patients, irrespective of the fact that the accompanying list of patients tabulation had a total of 127 patients.* Thus, the FDA reviewer argues, in addition of terminating the trial after an interim look, it is unclear whether the sponsor conducted an interim analysis, or several interim analyses, in subject populations ranging from 100 subjects, 119 subjects or 127 subjects.

As stated in Page 15 of the FDA statistical review, Dr. M. Al-Osh based his adjustment of statistical significance on the conduction of two interim analyses. One performed after 119 subjects were enrolled and completed the two week period and a second interim look after the final 151 subjects completed the trial. **Based on the FDA statistician reviewer calculations, the statistical significance for 851-6 efficacy results should be adjusted to a p-Value level of 0.018 (see statistician reviewer, Page 26).** Accordingly, **this reviewer will use this p-Value of 0.018 for assessments of the 851-6 efficacy results.**

*(e) Appropriate Efficacy Analyses.* In the following Intent-to-Treat analysis, the FDA statistician reviewer includes all 151 randomized patients and presents the results as expressed in the two primary endpoints, i.e., mean bowel movements