

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-551

**ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE**

RECEIVED

JUN 11 2003

FDR/CDER

June 10, 2003

Robert L. Justice, MD, MS
Food and Drug Administration
Director
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Fishers Document Room 8B-45
5600 Fisher Lane
Rockville, MD 20857

NOOO(())
NEW CORRESP

Re.: NDA 21-551 Half Lytely® (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets)

Patent Certification

Dear Dr. Justice:

This is in response to your letter dated June 5, 2003 regarding the treatment of Braintree Laboratories, Inc.'s new drug application (NDA) for Half Lytely® (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets) as a 505(b)(2) application based on Braintree's reliance on the OTC monograph for support of the bisacodyl portion of Half Lytely.

We understand that because this application will be treated by the Agency as a 505(b)(2) application, we are required to submit a patent certification pursuant to 21 CFR § 314.50(i). Accordingly, by this letter, the undersigned hereby certifies that in the opinion and to the best knowledge of Braintree Laboratories, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs. 21 CFR § 314.50(i)(1)(ii).

Sincerely,



Vivian A. Caballero
Director, Regulatory Affairs

for 505(b)(2)

November 21, 2002

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

Re.: NDA 21-551; Half Lytely® (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets)

Dear Ms. Kacuba:

In accordance with 21 CFR § 314.53(3), please be advised currently there are no patents which claim the above noted drug product or which claim a method of using the above noted drug product.

On October 25, 2002 Braintree Laboratories filed a method of use patent application for Half Lytely®.

If you have any additional questions, please call me.

Sincerely,



Vivian A. Caballero
Director, Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # 21-551 SUPPL # N/A

Trade Name: Half Lytely® Bowel Prep —

Generic Name: PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets

Applicant Name: Braintree Laboratories, Inc.

HFD # HFD-180

Approval Date If Known: May 10, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

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

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

YES / / NO / /

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

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

d) Did the applicant request exclusivity?

YES /___/ NO /X/

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

e) Has pediatric exclusivity been granted for this Active Moiety?

No

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

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

YES /___/ NO /_X_/ (Bisacodyl is marketed under the 1989 Tentative Final OTC Laxative Monograph)

If yes, NDA # _____ Drug Name _____.

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

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

YES /___/ NO /X/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA# _____

NDA# _____

2. Combination product.

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

YES /X/ NO /___/

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

NDA# 19-797 NuLyteLy (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution) 4 Liters and 1 gallon sizes. (Proposed product is 2L of PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution. Bisacodyl is marketed under the 1989 Tentative Final OTC Laxative Monograph).

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

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

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

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

YES /X/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are

published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES /X/ NO /___/

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

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol F38-13/14

Protocol F38-20

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

Investigation #1
IND # 28,306 YES /X/ NO /___/ Explain: _____

Investigation #2
IND # 57,673 YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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

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

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

YES /___/ NO /X/

If yes, explain: _____

{See appended electronic signature page}

Tanya Clayton
Regulatory Project Manager

Joyce Korvick, M.D.
Deputy Division Director

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

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

/s/

Tanya Clayton
5/10/04 02:54:03 PM

Joyce Korvick
5/10/04 02:55:39 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA #: 21-551 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: November 10, 2004 Action Date: AE-May 10, 2004

HFD-180 Trade and generic names/dosage form: Half-Lytely Bowel Prep — EG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets

Applicant: Braintree Laboratories, Inc. Therapeutic Class: 3S

Indication(s) previously approved: N/A

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

Number of indications for this application(s): 1

Indication #1: Bowel cleansing prior to colonoscopy

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

Yes: Please proceed to Section A.

XXXX No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

- Formulation needed
- Other: _____

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Other: _____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

HFD-950/Grace Carmouze

(revised 9-24-02) FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-950 301-827-7777

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

/s/

Tanya Clayton
4/6/04 05:13:35 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA #: 21-551 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: August 16, 2002 Action Date:

HFD-180 Trade and generic names/dosage form: Half-Lytely Bowel Prep System (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets)

Applicant: Braintree Laboratories, Inc. Therapeutic Class: 3S

Indication(s) previously approved: N/A

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

Number of indications for this application(s): 1

Indication #1: Bowel cleansing prior to colonoscopy

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

Yes: Please proceed to Section A.

XXXX No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

Formulation needed

Other: _____

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Other: _____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Health Project Manager

cc: NDA

HFD-950/ Terrie Crescenzi

HFD-960/ Grace Carmouze

(revised 9-24-02) FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Alice Kacuba
6/16/03 05:54:46 PM

Debarment Certification

Braintree Laboratories certifies it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 305(a) or (b)], in connection with this New Drug Application.



Vivian A. Caballero
Director, Regulatory Affairs

8-9-02

Date

BRAINTREE LABORATORIES, INC.
60 Columbian Street West
P.O. Box 850929
Braintree, MA 02185-0929
(781) 843-2202

2nd cycle

NDA ACTION PACKAGE CHECKLIST

Application Information

NDA 21-551 (2 nd Cycle Review)	
Drug: Half Lytely and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl delayed release tablets)	Applicant: Braintree Laboratories, Inc.
RPM: Tanya Clayton	HFD-180 Phone 301-827-4005
<div style="background-color: black; width: 100px; height: 15px;"></div>	Reference Listed Drug (NDA #, Drug name): NDA 21-551/HalfLytey and Bisacodyl Tablets Bowel Prep Kit
❖ Application Classifications:	
• Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Date	
June 16, 2003 (1 st cycle) May 10, 2004 (2 nd cycle)	
❖ Special programs (indicate all that apply)	
<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	
❖ User Fee Information	
• User Fee	<input checked="" type="checkbox"/> Paid
• User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	
<input checked="" type="checkbox"/> Verified	
❖ Patent	
• Information: Verify that patent information was submitted	<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (i) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will	<input type="checkbox"/> Verified

not be infringed (certification of notification and documentation of receipt of notice).

❖ Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA, 1 st cycle September 23, 2002)	X (1 st cycle) N/A (2 nd review cycle)
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE June 16, 2003
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X (in the June 16, 2003 AE letter to the firm)
• Most recent applicant-proposed labeling (dated November 6, 2003 and May 7, 2004)	X
• Original applicant-proposed labeling (dated August 15, 2002)	X
• Labeling reviews (Office of Drug Safety trade name review)	X (DMETS tradename)
• ODS DMETS- April 9, 2004	X (DDMAC)
• ODS DDMAC - April 15, 2004	
• Other relevant labeling (e.g., most recent 3 in class)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X (in the June 15, 2003 AE letter to the firm and May 4, 2004 fax to the firm)
• Applicant proposed (November 6, 2003 and May 7, 2004)	X
• Reviews	X (ODS DMETS tradename)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	May 5, 2004
• Documentation of discussions and/or agreements relating to post-marketing commitments	Requested May 5, 2004 Sponsor accepted May 7, 2004
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
Minutes of Meetings	
• Protocol discussion meeting (August 25, 1993)	X

• Pre-NDA meeting (October 5, 1998)	X
• Filing meeting (October 2, 2002)	X
• Pre-Approval Safety Conference	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)-Tentative Final Monograph	X
Summary Application Review	
❖ Summary Review (e.g., Office Director, Division Director, Medical Team Leader)	Deputy Division Director- May 10, 2004
Clinical Information	
❖ Clinical review (June 10, 2003; March 31, 2004)	X
❖ Microbiology (efficacy) review	N/A
❖ Safety Update review (included in June 10, 2003 and March 31, 2004)	X
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
❖ Statistical review (May 12, 2003)	X
Biopharmaceutical (May 16, 2003)	X
❖ Controlled Substance Staff review and recommendation for scheduling	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC reviews (May 8, 2003, May 20, 2003, March 24, 2004)	X
❖ Environmental Assessment	
• Categorical Exclusion – In cmc review dated (May 8, 2003)	X
• Review & FONSI	N/A
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Micro (validation of sterilization & product sterility)	N/A
❖ Facilities inspection (provide EER report)	Completed April 23, 2003 - Acceptable
❖ Methods validation	Requested in June 16, 2003 Action Letter
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review, including referenced IND reviews (November 13, 2002)	X
❖ Nonclinical inspection review summary	N/A
Statistical review of carcinogenicity studies	N/A
CAC/ECAC report	N/A

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

DATE: 5/5/04

FROM: Joyce A Korvick, MD, MPH
DGCDP/ODE III

SUBJECT: Director (Deputy) Summary Approval Comments
NDA 21-551

APPLICANT: Braintree Laboratories Inc.

DRUG: Four 5-mg bisacodyl enteric coated tablets
PLUS
a white powder for reconstitution (210 g PEG-3550, 2.86 g sodium bicarbonate, 5.6 g chloride, and 0.74 g potassium chloride and 1.0 g flavoring ingredient)

REGULATORY RECOMMENDATIONS:

The division recommends that this application be approved this cycle with one phase IV commitment:

- the applicant needs to provide the data regarding the degradation of the bisacodyl in the acid stage and continue to develop an appropriate acid stage as a part of the complete dissolution method. The time frame for fulfillment of this Phase IV commitment should be within a year of approval.

I. Background:

This is the second review cycle for NDA 21-551. The outstanding issues as outlined in the approvable letter (6/16/03) were as follows:

1. draft labeling be revised as indicated in the approvable letter (additional safety information is sought);
2. the rationale for choosing the conditions for the proposed *in-vitro* dissolution method are unclear. Data supporting the proposed conditions is needed before the method can be finalized. Therefore, data to support the dissolution method conditions must be submitted.

Previously, Braintree Laboratories, Inc. submitted NDA 21-551 on August 15, 2002 (received August 16, 2003) for Half-Lytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets) Bowel Prep — for the proposed indication of bowel cleansing prior to colonoscopy.

This product consists of 4 (5 mg) bisacodyl tablets and a jug of 2 Liters of NuLytely (PEG 3350 for oral solution.

— The bisacodyl tablets are to be administered first. Upon having the first bowel movement or 6 hours later, the patient is to drink the 2 Liters NuLytely (reconstituted) at a rate of 240 mL every ten minutes. —

PEG 3350 is an active ingredient of GoLytely and NuLytely currently on the market. It acts as an osmotic agent inducing diarrhea and thereby cleansing the bowel prior to colonoscopy. PEG 3350 has been reported to be minimally absorbed in vivo (<0.1%) and the absorbed PEG 3350 is mainly excreted unchanged in the urine.

Bisacodyl is a Category I OTC laxative agent formulated as an enteric-coated 5-mg tablet for treatment of occasional constipation in the dose range of 5-15 mg for adults. A single administration of 20 mg has been reported for use in preparation of surgery or for the colonic X-Ray and endoscopic examination.

II. Discipline Review summary and commentary:

A. OPDRA/DDMAC/DMETS:

During the first cycle DMETS review did NOT recommend the use of the proposed proprietary name Half Lytely Bowel Preparation — (the applicant was notified)

The primary concerns raised were related to the potential for “half” to be misinterpreted as directions for the for product use as opposed to “Half” being part of the propriety, and the packing configuration for Half Lytely Bowel Preparation — For example, a prescription written as “1/2 Lytely Use as directed. Dispense #1” maybe misinterpreted to mean the patient should only take one half of a “Lytely” product.

DMETS had no concerns with the promotional aspects of the propriety name Half Lytely Bowel Preparation — ; however, DMETS is concerned that the name may be misleading to practitioners and result in medication errors. In this case the patient might only take fifty percent of NuLytely, GoLytely, or Colyte without the bisacodyl tablets and may not achieve the expected outcome resulting in a delay of the procedure.

Further, the Nomenclature Committee recommended the use of the term “kit” instead of

—
—
— Therefore, “kit” is more widely recognized and prompts the practitioner to ensure all components are present and used together.

In the second review cycle Braintree revised the name as follows "HalfLyte[®] and Bisacodyl Tablets Bowel Prep Kit." This addressed the second issue of the kit in the name and is acceptable. The DMETS continued to have the same concerns regarding confusion with previous product naming. The division weighed the DMETS comments and decided to agree to the name in this review. Safety issues with possible substitutions and the overall state of the nomenclature among bowel prep kits. Firstly, substitution with other products would not lead to a safety issue, as the worst case could be half the dose of other formulations without the bisacodyl tablets. The following table illustrates the contents of these liquid preparations. Thus, an under dosing would potentially lead to an inadequate preparation and is not a safety issue. Secondly, regarding the name confusion, it is unclear to the division how other currently approved drugs are not confused. If Nulyte were given instead of Colyte a patient would get twice the amount of the PEG portion of the solution. If on the other hand a patient received Golyte instead of Nulyte they would receive a sulfur-containing product. These scenarios would have more serious implications. Finally, there are many OTC products that surgeons and gastroenterologists use labeled Fleets Prep Kit # 2, etc. One might conclude that this is a more difficult situation because there is no pharmacist involved and patients may fail to obtain the proper kit.

Contents of PEG-Prep Products

	Dosing Volume	PEG-3350	Na bicarbonate	NaCl	KCl	Na sulfate
Half-Lyte	2L	210g	2.86g	5.6g	0.74g	NA
Nulyte	4L	420g	5.72g	11.2g	1.48g	NA
Golyte	4L	236g	6.74g	5.86g	2.97g	22.74g
Colyte	4L	240g	6.72g	5.84g	2.98	22.74g

The division believes that ½ lyte will not be confused with other products that have specific prefaces such as NU-, GO- and CO. The package is a complete kit with very clear labeling regarding what is to be taken and how it is to be mixed by the patient. Therefore, it is acceptable to the division to approve the name as currently proposed in this second cycle label.

B. Chemistry:

The first cycle chemistry review was completed (5/20/03) and a list of deficiencies was communicated to the applicant. These included:

- 1.) The applicant should provide an adequate rationale for the dissolution method proposed. It is recommended the applicant use the USP delayed release method. This issue could be addressed as a Phase IV commitment within six months of approval of the application.
- 2.) Include the excipients forming part of the Bisacodyl tablets in the "Description" section of the label for the drug product.
- 3.) How supplied section should list the container used for the Bisadcodyl tablets.
- 4.) The storage temperature for the bottles should be included in the label. The storage statement should reflect the USP Controlled Room temperature

correctly: "20-25°C (68-77°F). Excursions permitted between 15-30°C (→ 86°F)."

- 5.) The name for the tablets should include "delayed release" all through the label. The recommendations for the tradename from the Labeling and Nomenclature Committee were to substitute the use of "Bowel Prep Kit" for "Bowel Prep" —

These issues were resolved in a satisfactory manner during this second cycle. Sponsor proposed a rationale for the dissolution method proposed which was found acceptable to the reviewers, however, they recommended a Phase IV commitment which is as follows: Braintree can continue to use the USP disintegration method currently employed as an interim method. However, the applicant needs to provide the data regarding the degradation of the bisacodyl in the acid stage and continue to develop an appropriate acid stage as a part of the complete dissolution method. The time frame for fulfillment of this Phase IV commitment should be within a year of approval.

The chemistry reviewers found this application could be approved.

C. Pharmacology/Toxicology:

The following is a quote from the pharm/tox reviewer's review. "The safety of the PEG and electrolyte components in Halflytely are well established through its clinical and postmarketing experience as NuLytely. Bisacodyl is also approved (non-prescription drug) as a Category I OTC laxative at doses of 5-15 mg/day. In addition, the proposed single dose of 20 mg of bisadcodyl, when used as part of a bowel-cleansing regime is also within the limit described in 21 CFR 334.66 (d)(3)(III)(a). Therefore, from a preclinical standpoint, there is no safety concern of the proposed Halflytely Bowel Prep System." From a pre-clinical standpoint it was recommended that this NDA "may be approved" during the first cycle.

D. Biopharmaceutics:

No new pharmacokinetic (PK) studies were conducted to support this NDA. Half Lytely is essentially NuLytely + bisacodyl, therefore reference is made to that NDA. Bisacodyl is an OCT product covered by a USP monograph. Because it is not absorbed, the dissolution specifications will be the basis upon which to determine its "bioequivalence". Dissolution data for 3 bisacodyl tablet lots using a modified USP method was submitted (bisacodyl delayed release tablet is a monograph in USP). The rational for selection of the dissolution method/ parameters has not been provided. The proposed dissolution and specifications should be used on an interim basis until an adequate rationale is provided for choosing conditions employed in the proposed method. (See chemistry comments above during the second cycle review).

It was concluded in this review that significant drug-drug interaction between bisacodyl and PEG 3350 is unlikely due to the lack of absorption.

The Biopharmaceutics review stated that the NDA is acceptable, since the applicant provided adequate rationale for the dissolution method.

E. Clinical Efficacy/Safety:

During the first cycle review the efficacy of the kit was deemed to have been demonstrated by the medical reviewer and team leader. While the overall safety of this product, based upon the clinical trials data submitted, was acceptable to the medical reviewer, the applicant failed to address reports in the literature of serious adverse events. This second cycle focused on the requested safety wording. The following briefly outlines the efficacy and safety from the first review cycle. The final wording of the adverse event section will be discussed under labeling section of this review.

This application included 2 pivotal studies (F38-13/14 and F38-20) and 2 supportive studies (F38-15 and F38-23). Both pivotal studies were carried out under a similar design using a randomized, single-blinded (investigator), active control (4 L NuLytely). Each pivotal trial utilized 2 different centers, for a total of 4 centers. Each study enrolled 200 patients. Physicians rated the preparation according to the interference of feces for an adequate colonoscopy exam, as “excellent” (no interference), “good” (minor interference), “fair” (interference but able to solve) and “poor” (unable to perform colonoscopy). In the subsequent analyses, the applicant compared the proportion of “successful” (excellent + good) and “unsuccessful” (fair + poor) in patients given the 2L+bis, and patients given 4L (NuLytely).

The Intention to Treat results are listed below:

Rating	4L NuLytely	2L + bis
Successful	90% (86)	86% (81)
Unsuccessful	10% (10)	14% (13)
Chi Sq-value = 0.52, p = 0.47		
Successful	78% (76)	80% (74)
Unsuccessful	22% (21)	20% (19)
Chi Sq-value = 0.52, p=0.58		

EFFICACY

Statistical:

The applicant failed to pre-specify the delta for the non-inferiority studies, instead relied solely on the p-value as a determinant of equivalence. The statistical reviewer analyzed the equivalence issues and found that the lower limit of the confidence interval for the comparison of Half Lytely to NuLytely for both studies was approximately -15% for Half Lytely (see statistical review for complete details). Since this delta was not pre-specified it is unclear as to its

statistical significance. The success rates are similar though strict equivalence was not demonstrated.

Clinical:

The clinical reviewer continues to comment on the primary efficacy analysis in two areas. First, from a clinical point of view this combination 2L+bis is probably as effective as Nu Lytely. This is supported by the fact that placebo studies have been carried out in the literature and colonoscopy was successful in from 0 – 15% of patients. Therefore, this combination is clinically effective. Secondly, there are no data presented by the applicant in the pivotal trials regarding the contribution of each component of the Half Lytely — . The applicant argues that bisacodyl by itself is not effective, therefore it was not included in the treatment arms of either study. This may be true, however, given the data presented by the applicant the contribution of each drug component to the efficacy of the HalfLytely — is uncertain, and should not be claimed as known in the label or in promotional announcements.

SAFETY:

Clinical:

The medical reviewer states that the majority of the reported adverse events are non-serious. The majority of events were “expected” as seen with a bowel cleansing system, such as nausea, vomiting, abdominal fullness, and abdominal cramping (for complete details see medial officer review). There were two serious AEs (Hematemesis, rectal bleeding). These AEs resolved spontaneously and were included by the applicant as non-serious.

The safety update was incomplete and submitted very late in the NDA cycle allowing inadequate time for dialogue with the applicant. Omitted from the update are 2 deaths associated with GoLyteLy in patients with end-stage renal disease, reported in the February BJU, 2003. The same article reported the development of tonic-clinic seizures after administration of GoLyteLy in a 62-y old female who was on treatment with a diazyde for hypertension. Her serum sodium before colonoscopy was 138 mmol/l and decreased to 116 after colonoscopy. She required intensive care treatment and fully recovered from the serious AE. Two deaths reported in the safety update are of concern.

The Medical reviewer states that the Half Lytely Bowel Prep System shows an acceptable risk benefit. However, the applicant’s assessment of the safety data is incomplete. The reports of serious AEs associated with PEG-3350, including death, should be incorporated in the amended label! —

F. Labeling Comments:

The Division's second cycle review of the labeling was in general agreement with that which was proposed by the applicant. However, the applicant did not include the serious adverse events which included literature reports of death and seizure. The division requested the following be added to the label under the adverse event section:

"Published literature contains isolated reports of serious adverse reactions following the administration of PEG-ELS products in patients over 60 years of age. These adverse events include upper GI bleeding from Mallory-Weiss syndrome, esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butter-fly-like" infiltrate on chest X-ray after vomiting and aspirating PEG."

"In addition, during administration of 4L PEG-3350 bowel cleansing preparation the following serious adverse events were seen: two deaths in end-stage renal failure patients who developed diarrhea, vomiting, dysnatremia; tonic-clonic seizures in patients with and without prior history of seizures."

In a tele-con with Braintree, May 5, 2004, the sponsor found this acceptable with the following qualifications:

That it be clear that these events were reported for the 4 L products and that the events of deaths and seizure were not seen the clinical studies data submitted to the NDA. This was agreeable with the division and the following additions were made:

"Published literature contains isolated reports of serious adverse reactions following the administration of 4L PEG-ELS products in patients over 60 years of age. These adverse events include upper GI bleeding from Mallory-Weiss syndrome, esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butter-fly-like" infiltrate on chest X-ray after vomiting and aspirating PEG."

"In addition, during administration of 4L PEG-3350 bowel cleansing preparation the following serious adverse events were seen: two deaths in end-stage renal failure patients who developed diarrhea, vomiting, dysnatremia; tonic-clonic seizures in patients with and without prior history of seizures." These adverse events have not been reported in the HalfLyte clinical trials.

This Division agreed with the proposal and requested a final proposed label form Braintree which included these changes.

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/s/

Joyce Korvick
5/10/04 08:04:54 AM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: May 5, 2004

APPLICATION NUMBER: NDA 21-551, HalfLyte^{ly} and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, potassium chloride for oral solution and bisacodyl delayed-release tablets)

BETWEEN:

Name: Vivian Caballero, Director, Regulatory Affairs,
Dr. Mark Cleveland, Director, Regulatory Affairs
Dr. Russ Pelham, Director, Pharmacology/Toxicology
Stephanie
Phone: 781-843-2202
Representing: Braintree Laboratories

AND

Name: Tanya Clayton, Regulatory Project Manager
Dr. Joyce Korvick, Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Robert Prizont, Medical Reviewer
Dr. Maria Ysern, Chemistry Reviewer
Phone: 301-827-7481
Representing: Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Discussion of Proposed Labeling and Tradename

This purpose of this teleconference was to speak with the Sponsor concerning their proposed labeling and tradename. Dr. Korvick led the conversation by explaining the rationale for the addition of Adverse Event information we requested in the package insert per our May 4, 2004 fax to the Sponsor. Dr. Cleveland responded to Dr. Korvick with his rationale as to why Braintree believes the addition is not necessary. This topic concluded with the firm agreeing to make the addition along with an additional sentence being added stating that none of the events mentioned has been reported with Halflyte^{ly}.

The next topic for discussion was the tradename. DMETS did not approve the tradename, however, Dr. Korvick informed the Sponsor that the Division has decided to override DMETS and accept Halflyte^{ly} as the tradename. The teleconference was followed up with the Sponsor agreeing to fax us a copy of the revised of the label/package insert as well as a commitment to make the requested changes on the final printed labeling.

Tanya Clayton, B.S.
Consumer Safety Officer

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/s/

Tanya Clayton
5/10/04 12:34:15 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 5, 2004

To: Vivian Caballero/Mark Cleveland	From: Tanya D. Clayton, BS Regulatory Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-4005
Subject: NDA 21-551	

Total no. of pages including cover: 2

Comments:

Please find attached the Division's recommendation for a Phase IV commitment.

Best regards

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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The Division agrees that you can continue to use the USP disintegration method currently employed as an interim method. However, you need to provide the data regarding the degradation of the bisacodyl in the acid stage and continue to develop an appropriate acid stage as a part of the complete dissolution method.

The time frame for fulfillment of this Phase IV commitment should be within a year of approval.

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/s/

Tanya Clayton
5/5/04 01:35:02 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 4, 2004

To: Vivian Caballero/Mark Cleveland	From: Tanya D. Clayton, BS Regulatory Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-4005
Subject: NDA 21-551	

Total no. of pages including cover: 2

Comments:

Please find attached the Divison's recommendation for the Adverse Event Section of your proposed label. Any questions regarding this recommendation can be discussed at tomorrow's teleconference.

Best regards

Document to be mailed: YES NO

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The Division recommends that you include the following statements in the adverse event section of the proposed label:

Published literature contains isolated reports of serious adverse reactions following the administration of PEG-ELS products in patients over 60 years of age. These adverse events include upper GI bleeding from Mallory-Weiss syndrome, esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butter-fly-like" infiltrate on chest X-ray after vomiting and aspirating PEG.

In addition, during administration of 4L PEG-3350 bowel cleansing preparation the following serious adverse events were seen: two deaths in end-stage renal failure patients who developed diarrhea, vomiting, dysnatremia; tonic-clonic seizures in patients with and without prior history of seizures.

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/s/

Tanya Clayton
5/4/04 02:47:54 PM
CSO



NDA 21-551

DISCIPLINE REVIEW LETTER

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Director, Regulatory Affairs
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your August 15, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Half Lytely Bowel Prep (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and biscodyl tablets).

We also refer to your submission dated November 6, 2003.

Our review of your proposed tradename is complete, and we have the following concerns:

We do not recommend use of the proprietary name HalfLytely and Bisacodyl Bowel Prep Kit. We are still concerned with the potential for confusion among practitioners (e.g., prescribers or dispensers) and medication errors with regards to NuLytely, GoLytely, Colyte and HalfLytely. The name "HalfLytely" may imply that the proposed product is half the strength or volume of GoLytely and Colyte.

We note that the objectives of the market research studies (F38-MR1 and F38-MR2) did not address our concerns with regards to the potential confusion of HalfLytely Bowel Prep and the currently marketed products NuLytely, GoLytely, and Colyte. Additionally, we are unsure if a comprehension study is the appropriate tool to use to determine if the proprietary name "HalfLytely" has any impact upon the prescribing practices or interpretation of prescriptions by healthcare practitioners.

Please consider proposing an alternate propriety name.

NDA 21-551

Page 2

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Tanya Clayton, B.S., Consumer Safety Officer, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

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

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/s/

Brian Strongin
4/19/04 08:14:28 AM

MEMORANDUM

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

DATE: April 21, 2004
FROM: Maria Elena Ysern, MSc, Review Chemist, HFD-180
THROUGH: Liang Zhou, PhD, Chemistry Team Leader for The Division of Gastrointestinal and Drug Coagulation Products, HFD-180
SUBJECT: NDA 21-551. HalfLyte[®] (PEG-3350, sodium Chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets.
TO: NDA 21-551

The dissolution method for testing Bisacodyl Delayed Release tablets was also reviewed by the office of Clinical Pharmacology and Biopharmaceutics which requested from the company that they develop an acid resistance stage. Braintree explained during telecoms 04/05/04 and 04/07/04 that

This justification, although found acceptable, should be supported by data.

Braintree can continue to use the USP disintegration method currently employed. However, the applicant needs to provide the data regarding the degradation of the bisacodyl and continue to develop an appropriate dissolution method within a year's time frame as a Phase 4 post-marketing commitment.

CC:
HFD-180/ MYsern
HFD-180TClayton
HFD-180/LZhou
HFD-180/Division Files
HFD-180/SDoddapaneni

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/s/

Maria Ysern
4/21/04 02:30:11 PM
CHEMIST

Liang Zhou
4/21/04 02:39:24 PM
CHEMIST

Tanya: This memo was consulted with Biopharm. We will
need to get an agreement from the applicant
if the division takes an AP action.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 870) Tracking/Action Sheet for Formal/Informal Consults		
From: Tien-Mien Chen, Ph.D. (HFD-870)		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission		
DATE: 04/16/04	IND No.: Serial No.:	NDA No. 21-551 (N-000)	DATE OF DOCUMENT 04-07-04	
NAME OF DRUG [Half Lytely]	PRIORITY CONSIDERATION		Date of informal/Formal Consult: 04-07-04	
NAME OF THE SPONSOR: [Braintree]				
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE				
<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED				
<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)				
<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input checked="" type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input type="checkbox"/> OTHER (SPECIFY BELOW): []				
REVIEW ACTION				
<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)				
<input type="checkbox"/> Oral communication with Name: [] <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: []				
<input type="checkbox"/> Formal Review/Memo (attached) <input checked="" type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (SPECIFY BELOW): []				
REVIEW COMMENT(S)				
<input checked="" type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR				
COMMENTS/SPECIAL INSTRUCTIONS: <u>Note: ADDENDUM TO THE PREVIOUS OCPB 04-02-04 REVIEW</u>				
<p>[X] Telecons with Braintree were held on 04/05/04 and 04/07/04 regarding the Agency's 02/06/04 IR letter regarding dissolution methodology and data in acid resistance stage. During these discussions and in a fax submitted on 04/07/04, Braintree explained that</p> <p style="text-align: right;">Braintree's correspondence in the 04/07/04 fax is attached</p> <p>in Appendix.</p>				
RECOMMENDATION: Braintree's justification for not developing an acid resistance stage was found reasonable. Therefore, Braintree can continue to use the USP disintegration method employed currently for acid resistance stage.				
SIGNATURE OF REVIEWER: <u>Tien-Mien Chen, Ph.D.</u>		Date <u>04/16/04</u>		
SIGNATURE OF TEAM LEADER: <u>Suresh Doddapaneni, Ph.D.</u>		Date <u>04/16/04</u>		
CC.: HFD # [180]; TL: [SD]		Project Manager: <u>T. Clayton</u> Date <u>04/16/04</u>		

NDA 21-551 (N-000; BM) for Half Lytely

Appendix

Sponsor's Correspondence Dated 04/07/04



VIA FACSIMILE (301) 443-9285

April 7, 2004

Tanya Clayton
Food and Drug Administration
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Fishers Document Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-551, HalfLyte[®] (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets)

Request for Information

Dear Ms. Clayton:

Braintree Laboratories has determined that bisacodyl degrades in acid media. Therefore, an assay as requested in FDA's 1/20/04 and 2/6/04 Information Requests cannot be developed.

Braintree Laboratories has submitted a procedure in the HalfLyte[®] NDA (NDA 21-551; see SOP170, Vol. 1.6.3, page 989-995). This assay is performed using the disintegration test as found in the USP Bisacodyl Tablets monograph (See USP27 pages 251-252, and method <701> page 2302). According to this procedure, 6 tablets are placed into each of 6 separate tubes within the basket-rack disintegration assembly in an acid media. The tablets are required to be intact, by visual inspection.

According to Braintree SOP:

As we discussed today by telephone, experiments performed by Braintree Laboratories have revealed that

It is our opinion that an assay for bisacodyl and related products cannot be reliably performed when acid media is used and that a method using acid media cannot be validated.

If you have any questions, please call me or Vivian Caballero at (781) 843-2202.

Sincerely,

Mark vB. Cleveland, Ph.D.
V.P., Scientific and Regulatory Affairs

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/s/

Tien-Mien Chen
4/16/04 12:49:36 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
4/16/04 02:13:08 PM
BIOPHARMACEUTICS

5 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

DATE RECEIVED: December 10, 2003

DUE DATE: March 10, 2003

ODS CONSULT #: 02-0187-1

PDUFA DATE: May 10, 2004

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

THROUGH: Tanya Clayton
Project Manager, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

PRODUCT NAME:

HalfLyte and Bisacodyl Tablets Bowel Prep Kit
(PEG-3350, Sodium Chloride, Sodium Bicarbonate, Potassium Chloride for Oral Solution) 210 g, 2.86 g, 5.6 g, 0.74 g and (Bisacodyl Tablets USP) 5mg

NDA SPONSOR:

Braintree Laboratories Inc.

NDA: 21-551

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

RECOMMENDATIONS:

1. DMETS does not recommend use of the proprietary name HalfLyte and Bisacodyl Tablet Bowel Prep Kit.
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review.

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

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

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Room 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 7, 2004

NDA#: 21-551

NAME OF DRUG: **HalfLytely and Bisacodyl Tablets Bowel Prep Kit**
(PEG-3350, Sodium Chloride, Sodium Bicarbonate, Potassium Chloride
for Oral Solution) 210 g, 2.86 g, 5.6 g, 0.74 g and (Bisacodyl Tablets USP) 5 mg

NDA SPONSOR: **Braintree Laboratories Inc.**

I. INTRODUCTION:

This review is in response to a request from the Office of Gastrointestinal and Coagulation Drug Products (HFD-180), to review the proprietary name HalfLytely and Bisacodyl Tablets Bowel Prep Kit regarding potential name confusion with other proprietary and established drug names. DMETS initially reviewed the proprietary name Half Lytely Bowel Preparation — and did not recommend use of the proposed name due to concerns that use of the word “Half” in the proprietary name HalfLytely Bowel Preparation System will increase the potential for medication errors due to name confusion with the currently marketed products, GoLytely, NuLytely, and Colyte. In response to DMETS’ review the sponsor has changed the proposed proprietary name to HalfLytely and Bisacodyl Tablets Bowel Prep Kit and also submitted a Market Research Study conducted by —

— The objective of the market research was to “determine if the proposed proprietary name ‘Half Lytely’ may be misinterpreted as directions for product administration of the bowel preparation ...” Revised container labels, carton and insert labeling for the HalfLytely and Bisacodyl Tablets Bowel Prep Kit were also submitted for review and comment.

PRODUCT INFORMATION

The HalfLytely and Bisacodyl Tablets Bowel Prep Kit consists of two drugs co-packaged together. Four bisacodyl 5 mg tablets are packaged together with the dry powder (for Oral Solution) combination of PEG-3350, Sodium Chloride, Sodium Bicarbonate, and Potassium Chloride. The dry powder component is reconstituted with water which results in a two liter oral solution. Half Lytely is indicated for bowel cleansing prior to colonoscopy. The patient takes four Bisacodyl 5 mg tablets which is followed by eight ounces of the oral solution (i.e., after a bowel movement or a maximum of six hours later) until all two liters of the solution have been consumed.

The dry powder contains the same ingredients found in NuLytely, which is also manufactured by Braintree Laboratories. However, the active ingredients of HalfLytely have been reduced by fifty percent in comparison to the ingredients in NuLytely. When reconstituted HalfLytely contains a total volume of 2 liters. The dose is identical (eight ounces every ten minutes until the entire contents of the

bottle are consumed (2 liters). The HalfLytely and Bisacodyl Tablets Bowel Prep Kit will be available as non-flavored and flavored solutions. The powder for reconstitution will be packaged in a carton comprised of a 2 L disposable jug (containing the dry powder for reconstitution) and Bisacodyl 5 mg tablets.

II. RISK ASSESSMENT:

A. SAFETY EVALUATOR RISK ASSESSMENT

The sponsor has requested a reconsideration of the proprietary name HalfLytely for the combination product containing PEG-3350, Sodium Chloride, Sodium Bicarbonate, and Potassium Chloride and four Bisacodyl Tablets. The proposed proprietary name initially reviewed by DMETS was *Half Lytely Bowel Preparation*. DMETS had concerns that the word "Half" could potentially be misinterpreted as directions for product use and/or be misleading to practitioners thereby resulting in medication errors. Although the sponsor has submitted a market research study in support of the proposed proprietary name "HalfLytely", they have also submitted a different proprietary name *HalfLytely and Bisacodyl Tablets Bowel Prep Kit*. DMETS will address the market research study conducted by _____ separately from the review of the proposed proprietary name HalfLytely and Bisacodyl Tablets Prep Kit.

1. _____ Market Research Studies (F38-MR1 and F38-MR2)

The sponsor indicated that the objective of the Market Research Studies was to determine if the proposed proprietary name "HalfLytely" could be misinterpreted as directions for product administration of the bowel preparation.

DMETS notes that the objective of the Market Research Studies F38-MR1 and F38-MR2 does not address the safety concerns outlined in our May 7, 2003 proprietary name review. DMETS had the following concerns:

- The word "Half" in the proprietary name *Half Lytely Bowel Preparation* will increase the potential for medication errors due to name confusion with the currently marketed products, GoLytely, NuLytely, Colyte, and Half Lytely especially when scripted with ambiguous instructions such as 'Use as Directed.'
- DMETS is concerned that the name may be misleading to practitioners and result in medication errors. Practitioners are familiar with NuLytely, GoLytely, and Colyte. The name "Half Lytely" may imply that the proposed product is half the strength or volume of NuLytely, GoLytely, or Colyte.

Although, the studies were geared toward identifying confusion with the "HalfLytely" they did not specifically target healthcare practitioners. The study format involved comprehension of the proposed labels and labeling for *Half Lytely Bowel Preparation* _____ mainly at the patient level. We note that approximately 104 of the 160 healthcare practitioners that were included in study F38-MR2 were licensed medical professionals who prescribe, dispense or administer drug. Despite the inclusion of these healthcare practitioners in this study their goal was to determine if the labels and labeling were clear and understandable to the user. Individuals who prescribe, dispense or administer

pharmaceutical products were not asked to assess what they thought the "Half Lytely Bowel Preparation" contained (i.e., ingredients) or what they thought the product HalfLytely contained (i.e., volume and or active ingredients).

In summary, these studies would need to be evaluated by the Office of Drug Safety's Division of Surveillance, Research, and Communication Support to determine if patients comprehend the directions. We note that the objectives of the Market Research Studies (F38-MR1 and F38-MR2) did not address the concerns of DMETS with regards to the potential confusion with Half Lytely Bowel Preparation System and the currently marketed products NuLytely, GoLytely, and Colyte. Additionally, DMETS is unsure if a comprehension study is the appropriate tool to use to determine if the proprietary name "HalfLytely" has any impact upon the prescribing practices or interpretation of prescriptions by healthcare practitioners.

2. HalfLytely and Bisacodyl Tablets Prep Kit Proprietary Name Review

The sponsor has proposed changing the proprietary name from *Half Lytely Bowel Preparation* to *HalfLytely and Bisacodyl Tablets Prep Kit*. The sponsor has developed a carton that contains the two components of the Preparation Kit. With regard to the revised proprietary name, "HalfLytely" refers to the individual dry powder component (containing PEG-3350, Sodium Chloride, Sodium Bicarbonate, and Potassium Chloride) whereas previously "HalfLytely" was the proposed name of the Kit containing both products. DMETS acknowledges that this change helps to more clearly identify the components of the Prep Kit. However, DMETS is still concerned with the potential for confusion among practitioners (e.g., prescribers or dispensers).

Braintree currently markets two dry powder products (NuLytely and GoLytely), in different concentrations that contain similar ingredients as HalfLytely except that GoLytely also contains sodium sulfate. The proposed product "HalfLytely" contains 50% of the ingredients found in NuLytely with a final volume that is 50% of NuLytely (4L). Although the HalfLytely product is half the strength and volume of NuLytely, it is not half the strength or volume of GoLytely or Colyte (similar product manufactured by Schwarz Pharma). Practitioners are familiar with NuLytely, GoLytely, and Colyte, the dosing volume and the fact that the expected results may be achieved with half a bottle. Additionally, these products are also 'bowel preps' even though the proprietary name does not include the words 'bowel prep.' Moreover, the proprietary name *HalfLytely and Bisacodyl Tablets Prep Kit* is long and practitioners are likely to abbreviate or inadvertently omit parts of the name. All of the aforementioned factors could contribute to the potential for confusion. For example, a prescription for "½ Lytely Prep Kit" or "½ Lytely Prep" could be misinterpreted as half of one of the Lytely products. If the four bisacodyl tablets were dispensed/given, then one half of NuLytely would be appropriate. However, any other substitution would not be equivalent. Since these products are generally dosed as 8 ounces every 10 minutes until rectal effluent is clear, patients may experience the expected results after using half a bottle. Adding a pharmacy auxiliary label that indicates the bottle contains more product than is prescribed and telling the patient to use only ½ bottle (approximately eight glasses) is plausible. This scenario could easily occur in an inpatient setting, where nursing staff would be measuring and providing the patient with the drug. Although, a prescription for "½ Lytely Prep Kit" or "½ Lytely Prep" should be clarified with the prescriber, if an inpatient institution has only

one of the currently marketed bowel preparation products on formulary, and the practitioner realizes that half the bottle could be effective, a call to clarify the order may not occur.

In summary, DMETS remains concerned that the proprietary name "HalfLyte" provides an opportunity for confusion with regards to the dose and product and increases the potential for medication errors between NuLyte, GoLyte, Colyte and HalfLyte.

B. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the revised container labels, carton and insert labeling of HalfLyte and Bisacodyl Tablets Bowel Prep Kit, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENTS

DMETS notes that the proprietary name HalfLyte is more prominently displayed than the other components of the name. Since the proposed proprietary name is *HalfLyte and Bisacodyl Tablets Bowel Prep Kit*, the entire name should be displayed with equal prominence. The current presentation makes Bisacodyl look like it is the established name for HalfLyte. Revise accordingly.

2. HALFLYTELY CONTAINER LABEL

No Comments at this time.

3. BISACODYL TABLETS CONTAINER LABEL

a. DMETS recommends :

b. There are no directions on the container, which inform the patient how to remove the tablets from the container (e.g., push through foil...). Revise accordingly.

c.

4. HALFLYTELY AND BISACODYL TABLETS CARTON LABELING

a.

i.

5. PACKAGE INSERT LABELING

DESCRIPTION Section

DMETS questions why the dose and administration is included in this section.
Please comment.

IV. RECOMMENDATIONS:

- A. DMETS does not recommend use of the proprietary name Half Lytely Bowel Preparation
- B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review.

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

Denise P. Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Denise Toyer
4/9/04 03:48:08 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/9/04 03:50:15 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF TELECON

DATE: April 7, 2004

APPLICATION NUMBER: NDA 21-551, HalfLyte and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, potassium chloride for oral solution and bisacodyl delayed-release tablets)

BETWEEN:

Name: Mark Cleveland, Ph.D.
Vivian Caballero
Brian Harrington, Ph.D.
Phone: 781-843-7932
Representing: Braintree Laboratories

AND

Name: Tanya Clayton, B.S., Consumer Safety Officer
Tien-Mien Chen, Ph.D., Biopharm Reviewer
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Biopharmaceutical Request for the proposed dissolution specification for acid stage of bisacodyl delayed release tablets.

This teleconference was in response to our information request dated January 20, 2004 and February 6, 2004, in which Dr Chen requested dissolution data at the acid resistance stage. The sponsors attempted to respond to Dr. Chen's request on February 27, 2004. However, the response was not acceptable because the sponsors provided dissolution data in buffer stage instead of the requested acid stage.

During this teleconference, the sponsors explained to Dr. Chen that the request is impossible to test because

_____ They further explained that using an acid media method cannot be validated.

Upon their explanation, Dr. Chen stated that he now understands the situation and that he would have to talk with his Team Leader before any decisions could be made.

The conversation closed by informing the sponsor that the final decision concerning this matter would be stated in the action letter.

Tanya Clayton, B.S.
Consumer Safety Officer

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/s/

Tanya Clayton
4/15/04 11:26:10 AM
CSO

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

**Clinical Pharmacology & Biopharmaceutics
(HFD 870)
Tracking/Action Sheet for Formal/Informal Consults**

From: Tien-Mien Chen, Ph.D. (HFD-870)

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the
specified IND/NDA submission

DATE: 03/26/04

IND No.:
Serial No.:

NDA No. 21-551
(N-000, AZ & BM)

DATE OF DOCUMENT
11/06/03, 02/27/04

NAME OF DRUG
[Half-Lytely]

PRIORITY CONSIDERATION

Date of informal/Formal
Consult: 12/19/03, 03/08/04

NAME OF THE SPONSOR: [Braintree]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE

- | | | |
|--|--|--|
| <input type="checkbox"/> PRE-IND | <input checked="" type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-
NDA/CMC/Pharmacometrics/Others) | <input type="checkbox"/> OTHER (SPECIFY BELOW):
[] |
| <input type="checkbox"/> PHASE IV RELATED | | |

REVIEW ACTION

- | | | |
|---|---|--|
| <input type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with
Name: [] | <input type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | <input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes
dated: [] | <input checked="" type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox | | <input type="checkbox"/> See submission cover letter |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | | <input type="checkbox"/> OTHER (SPECIFY BELOW):
[] |

REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS/SPECIAL INSTRUCTIONS:

[X] NDA 21-551 for Half-Lytely (PEG 3350 plus electrolytes and four bisacodyl 5 mg tablets) has been reviewed by the Agency and found to be approvable on 06/16/03. An OCPB comment (as one of the deficiencies) was conveyed in the approvable letter requesting the rationale and acceptable supporting data justifying the conditions of *in vitro* dissolution methodology for bisacodyl delayed release tablets.

On 11/06/03, the sponsor submitted a complete response. However, it was found that the acid resistance stage did not follow the drug release procedures described in USP 26/NF 21, sections <711> and <724> for enteric coated products. A telecon was held between the Agency and the sponsor to clarify this followed by an information request for dissolution data at acid resistance stage (for 2 hours) on 02/06/04. Please see Attachment 1 for details.

On 02/27/04, the sponsor responded to the above request. However, the submitted data contained additional dissolution data in buffer stage only and not in acid stage as requested. As such, data in acid resistance stage is still pending.

RECOMMENDATION:

From OCPB point of view, the submission is acceptable provided that the sponsor adequately addresses the deficiency outlined in the comment below. The dissolution method and dissolution specification will be finalized after such data outlined in the comment is submitted and reviewed by the Agency for acceptability. Until such time, the current method can be used on an interim basis.

COMMENT: (Needs to be sent to the sponsor)

Your response to the Agency's information request on 02/06/04 regarding dissolution data in acid stage contained data in the buffer stage only. Please provide information in the acid stage as follows:

In general, for enteric coated drug products, drug release procedures described in USP 26/ NF 21, sections <711> and <724> should be followed. This consists of testing in an acid stage (0.1 N HCl) for 2 hours followed by testing in the buffer stage. It appears that the proposed method is incomplete in that the product is subjected to buffer stage but not to acid stage.

Since the proposed method utilized apparatus 2 at 100 rpm in the buffer stage, additional testing should be carried out in 0.1 N HCl under the same conditions and a specification should be proposed for the acid stage as well.

SIGNATURE OF REVIEWER: Tien-Mien Chen, Ph.D.

Date 04/02/04

SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.

Date 04/02/04

CC.: HFD # [180]; TL: [SD]

Project Manager: T. Clayton Date 04/02/04

NDA 21-551 (N-000; BM) for Half Lytely

Appendix

Agency's IR Letter Dated 02/06/04



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 6, 2004

To: Vivian Caballero	From: Tanya Clayton Regulatory Project Manager
Company: Braintree Laboratories	Company: Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: 301-827-4005

Subject NDA 21-551- Information Request

:

Total no. of pages including cover: 2

Comments:

Please find the attached request, per our previous teleconference with Dr. Chen (Biopharm reviewer).

Best regards,
Tanya

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In general, for enteric coated drug products, drug release procedures described in USP 26/ NF 21, sections <711> and <724> should be followed. This consists of testing in an acid stage (0.1 N HCl) for 2 hours followed by testing in the buffer stage. It appears that the proposed method is incomplete in that the product is subjected to buffer stage but not to

acid stage.

Since the proposed method utilized apparatus 2 at 100 rpm in the buffer stage, additional testing should be carried out in 0.1 N HCl under the same conditions and a specification should be proposed for the acid stage as well.

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/s/

Tien-Mien Chen
4/2/04 01:43:53 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
4/2/04 02:21:25 PM
BIOPHARMACEUTICS

MEMORANDUM

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

DATE: March 16, 2004
FROM: Maria Elena Ysern, MSc, Review Chemist, HFD-180
THROUGH: Liang Zhou, PhD, Chemistry Team Leader for the Division of Gastrointestinal and Drug Coagulation Products, HFD-180
SUBJECT: NDA 21-551. Amendment.
TO: NDA 21-551

Braintree has submitted an Amendment to NDA 21-551 Half Lytely® Bowel Prep Kit (Peg-3350, sodium chloride, sodium bicarbonate, potassium chloride for oral solution and bisacodyl delayed release tablets) in response to a discipline review letter (dated May 29, 2003) in reference to NDA 21-2551, submitted in Aug 15, 2002.

Draft labeling for the package insert and components has been included. A kit has been developed to contain the components for the preparation. The name on the kit has been revised to "Half Lytely and Bisacodyl Tablets Bowel Prep Kit (peg-3350, sodium chloride, sodium bicarbonate, potassium chloride for oral solution and bisacodyl delayed-release tablets".

Bisacodyl tablets have been revised throughout. The bottle label and bisacodyl tablets have been revised with the specific established name for each component. The components contained in the kit have been listed on the outer package. The trade name has been revised to include the word "kit".

The applicant has provided some clarification of the proposed bisacodyl dissolution method, it has also been reviewed by the Division of Biopharmaceutics and additional information has been required. The method is still not adequate for the delayed release bisacodyl tablets and the update of the method can become a Phase IV commitment. The bisacodyl tablets are an already marketed product so there are less safety concerns but the methods need to be updated.

CC:
HFD-180/ MYsern
HFD-180TClayton
HFD-180/LZhou
HFD-180/Division Files

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/s/

Maria Ysern
3/24/04 04:35:20 PM
CHEMIST

Liang Zhou
3/24/04 04:45:46 PM
CHEMIST
The Phase IV will be included in Biopharm review.

MEMORANDUM OF TELECON

DATE: February 6, 2004

APPLICATION NUMBER: NDA 21-551, HalfLyte and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, potassium chloride for oral solution and bisacodyl delayed-release tablets)

BETWEEN:

Name: Vivian Caballero, Director, Regulatory Affairs
Phone: 781-843-7932
Representing: Braintree Laboratories

AND

Name: Tanya Clayton, B.S., Consumer Safety Officer
Tien-Mien Chen, Ph.D., Biopharm Reviewer
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Biopharmaceutical Request for the proposed dissolution specification for acid stage of bisacodyl delayed release tablets.

This purpose of this teleconference was to speak with Ms. Caballero concerning Dr. Chen's January 20, 2004 request (via fax) for dissolution data at the acid resistance stage. Dr. Chen further clarified his request to Ms. Caballero in which she agreed to forward it to the appropriate staff for a response. The conversation was also followed up with a fax stating the clarifications.

Tanya Clayton, B.S.
Consumer Safety Officer

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/s/

Tanya Clayton
4/15/04 11:46:37 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 6, 2004

To: Vivian Caballero	From: Tanya Clayton Regulatory Project Manager
Company: Braintree Laboratories	Company: Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: 301-827-4005
Subject: NDA 21-551- Information Request	

Total no. of pages including cover: 2

Comments:

Please find the attached request, per our previous teleconference with Dr. Chen (Biopharm reviewer).

Best regards,
Tanya

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In general, for enteric coated drug products, drug release procedures described in USP 26/ NF 21, sections <711> and <724> should be followed. This consists of testing in an acid stage (0.1 N HCl) for 2 hours followed by testing in the buffer stage. It appears that the proposed method is incomplete in that the product is subjected to buffer stage but not to acid stage.

Since the proposed method utilized apparatus 2 at 100 rpm in the buffer stage, additional testing should be carried out in 0.1 N HCl under the same conditions and a specification should be proposed for the acid stage as well.



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 20, 2004

To: Vivian Caballero	From: Tanya D. Clayton, BS Regulatory Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-4005

Subject: NDA 21-551/Information Request

Total no. of pages including cover: 2

Comments:

Please find attached 2 information requests from the Biopharm Reviewer.

Should you have any questions concerning this fax, please contact me at the number listed above.

Document to be mailed: YES NO

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Please provide the following information:

1. Raw and mean data on percent dissolved (tabulated) of the batch Nos. 852, 853, and 854.
2. Proposed dissolution specification for Bisacodyl delayed release tablets in acidic medium for 1 hour.



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 13, 2004

To: Vivian Caballero	From: Tanya Clayton
Company: Braintree Laboratories	Company: Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: 301-827-4005
Subject: NDA 21-551- Information Request	

Total no. of pages including cover: 1

Comments:

Please forward a copy of the previously submitted and proposed annotated labeling in MS Word to my attention. In your cover letter be sure to state that this is a Desk Copy.

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REQUEST FOR CONSULTATION

Division/Office):

FROM: Tanya Clayton, Regulatory Health Project Manager, HFD-180

Associate Director, Medication Error Prevention
Office of Drug Safety, HFD-400
(Sammie Beam-Rm. 6-34, PKLN Bldg.)

DATE December 4, 2003	IND NO.	NDA NO. 21-551	TYPE OF DOCUMENT Response to Approvable Letter	DATE OF DOCUMENT November 6, 2003
NAME OF DRUG Half Lytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride and bisacodyl tablets) Bowel Prep		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Cathartic	DESIRED COMPLETION DATE March 10, 2004

NAME OF FIRM: Braintree Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|---|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
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IV. DRUG EXPERIENCE

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
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V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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COMMENTS/SPECIAL INSTRUCTIONS:

Braintree has submitted a complete response to our Approvable Letter dated June 16, 2003 for NDA 21-551, Half Lytely Bowel Prep as a bowel cleansing agent prior to colonoscopy. The 6 month goal date for this NDA is May 10, 2004, with a Divisional Goal date for completed divisional reviews by April 12, 2004. Please complete the tradename review by March 10, 2004 in order for the review to be complete. Complete their reviews by the Division goal date. Thank you.

Attachments: Desk Copy of submission

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Tanya Clayton
12/4/03 12:57:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-551

Braintree Laboratories, Inc.
Attention: Vivian Caballero
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185-0929

Dear Ms. Caballero:

We acknowledge receipt on November 10, 2003 of your November 6, 2003 resubmission to your supplemental new drug application for Half Lytely® Bowel Prep (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets).

We consider this a complete, class 2 response to our June 16, 2003 action letter. Therefore, the user fee goal date is May 10, 2004.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Tanya Clayton
11/21/03 12:25:34 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 6/16/03

FROM: Joyce A Korvick, MD, MPH
DGCDP/ODE III

SUBJECT: Director (Deputy) Summary Approval Comments
NDA 21-551

APPLICANT: Braintree Laboratories Inc.

DRUG: Four 5-mg bisacodyl enteric coated tablets
PLUS
a white powder for reconstitution (210 g PEG-3550, 2.86 g sodium bicarbonate, 5.6 g chloride, and 0.74 g potassium chloride and 1.0 g flavoring ingredient)

REGULATORY RECOMMENDATIONS:

The division recommends that this application is approvable pending the following information:

1. draft labeling revised as indicated in the approvable letter (additional safety information is sought);
2. the rationale for choosing the conditions for the proposed *in-vitro* dissolution method are unclear. Data supporting the proposed conditions is needed before the method can be finalized. Therefore, data to support the dissolution method conditions must be submitted.

I. Background:

Braintree Laboratories, Inc. submitted NDA 21-551 on August 15, 2002 (received August 16, 2003) for Half-Lytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets) Bowel Prep — for the proposed indication of bowel cleansing prior to colonoscopy.

This product consists of 4 (5 mg) bisacodyl tablets and a jug of 2 Liters of NuLytely (PEG 3350 for oral solution.

The bisacodyl tablets are to be administered first. Upon having the first bowel movement or 6 hours later, the patient is to drink the 2 Liters NuLytely (reconstituted) at a rate of 240 mL every ten minutes. was sent to the applicant

PEG 3350 is an active ingredient of GoLytely and NuLytely currently on the market. It acts as an osmotic agent inducing diarrhea and thereby cleansing the bowel prior to colonoscopy. PEG 3350 has been reported to be minimally absorbed in vivo (<0.1%) and the absorbed PEG 3350 is mainly excreted unchanged in the urine.

Bisacodyl is a Category I OTC laxative agent formulated as an enteric-coated 5-mg tablet for treatment of occasional constipation in the dose range of 5-15 mg for adults. A single administration of 20 mg has been reported for use in preparation of surgery or for the colonic X-Ray and endoscopic examination.

II. Discipline Review summary and commentary:

A. OPDRA/DDMAC/DMETS:

DMETS review does NOT recommend the use of the proposed proprietary name Half Lytely Bowel Preparation — the applicant was notified)

The primary concerns raised were related to the potential for “half” to be misinterpreted as directions for the for product use as opposed to “Half” being part of the propriety, and the packing configuration for Half Lytely Bowel Preparation System. For example, a prescription written as “1/2 Lytely Use as directed. Dispense #1” maybe misinterpreted to mean the patient should only take one half of a “Lytely” product.

DMETS had no concerns with the promotional aspects of the propriety name Half Lytely Bowel Preparation — however, DMETS is concerned that the name may be misleading to practitioners and result in medication errors. In this case the patient might only take fifty percent of NuLytely, GoLytely, or Colyte without the bisacodyl tablets and may not achieve the expected outcome resulting in a delay of the procedure.

Further, the Nomenclature Committee recommended the use of the term “kit” instead of

Therefore, “kit” is more widely recognized and prompts the practitioner to ensure all components are present and used together.

B. Chemistry:

The chemistry review was completed (5/20/03) and a list of deficiencies was communicated to the applicant. These included:

- 1.) The applicant should provide an adequate rationale for the dissolution method proposed. It is recommended the applicant use the USP delayed release method. This issue could be addressed as a Phase IV commitment within six months of approval of the application.
- 2.) Include the excipients forming part of the Bisacodyl tablets in the “Description” section of the label for the drug product.

- 3.) How supplied section should list the container used for the Bisacodyl tablets.
- 4.) The storage temperature for the bottles should be included in the label. The storage statement should reflect the USP Controlled Room temperature correctly: "20-25°C (68-77°F). Excursions permitted between 15-30°C (— 86°F)."
- 5.) The name for the tablets should include "delayed release" all through the label. The recommendations for the tradename from the Labeling and Nomenclature Committee were to substitute the use of "Bowel Prep Kit" for "Bowel Prep — .

The chemistry reviewers found this application could be approved.

C. Pharmacology/Toxicology:

The following is a quote from the pharm/tox reviewer's review. "The safety of the PEG and electrolyte components in Halflytely are well established through its clinical and postmarketing experience as NuLyteLy. Bisacodyl is also approved (non-prescription drug) as a Category I OTC laxative at doses of 5-15 mg/day. In addition, the proposed single dose of 20 mg of bisacodyl, when used as part of a bowel-cleansing regime is also within the limit described in 21 CFR 334.66 (d)(3)(III)(a). Therefore, from a preclinical standpoint, there is no safety concern of the proposed Halflytely Bowel Prep

" From a pre-clinical standpoint it was recommended that this NDA "may be approved".

D. Biopharmaceutics:

No new pharmacokinetic (PK) studies were conducted to support this NDA. Half LyteLy is essentially NuLyteLy + bisacodyl, therefore reference is made to that NDA. Bisacodyl is an OCT product covered by a USP monograph. Because it is not absorbed, the dissolution specifications will be the basis upon which to determine its "bioequivalence". Dissolution data for 3 bisacodyl tablet lots using a modified USP method was submitted (bisacodyl delayed release tablet is a monograph in USP). The rationale for selection of the dissolution method/ parameters has not been provided. The proposed dissolution and specifications should be used on an interim basis until an adequate rationale is provided for choosing conditions employed in the proposed method.

It was concluded in this review that significant drug-drug interaction between bisacodyl and PEG 3350 is unlikely due to the lack of absorption.

The Biopharmaceutics review stated that the NDA is acceptable provided that the applicant submits an adequate rationale for the dissolution method and labeling recommendations are agreed upon.

E. Clinical Efficacy/Safety:

This application included 2 pivotal studies (F38-13/14 and F38-20) and 2 supportive studies (F38-15 and F38-23). Both pivotal studies were carried out under a similar design using a randomized, single-blinded (investigator), active control (4 L NuLytely). Each pivotal trial utilized 2 different centers, for a total of 4 centers. Each study enrolled 200 patients. Physicians rated the preparation according to the interference of feces for an adequate colonoscopy exam, as “excellent” (no interference), “good” (minor interference), “fair” (interference but able to solve) and “poor” (unable to perform colonoscopy). In the subsequent analyses, the applicant compared the proportion of “successful” (excellent + good) and “unsuccessful” (fair + poor) in patients given the 2L+bis, and patients given 4L (NuLytely).

The Intention to Treat results are listed below:

Rating	4L NuLytely	2L + bis
Successful	90% (86)	86% (81)
Unsuccessful	10% (10)	14% (13)
Chi Sq-value = 0.52, p = 0.47		
Successful	78% (76)	80% (74)
Unsuccessful	22% (21)	20% (19)
Chi Sq-value = 0.52, p=0.58		

EFFICACY

Statistical:

The applicant failed to pre-specify the delta for the non-inferiority studies, instead relied solely on the p-value as a determinant of equivalence. The statistical reviewer analyzed the equivalence issues and found that the lower limit of the confidence interval for the comparison of Half Lytely to NuLytely for both studies was approximately -15% for Half Lytely (see statistical review for complete details). Since this delta was not pre-specified it is unclear as to its statistical significance. The success rates are similar though strict equivalence was not demonstrated.

Clinical:

The clinical reviewer continues to comment on the primary efficacy analysis in two areas. First, from a clinical point of view this combination 2L+bis is probably as effective as Nu Lytely. This is supported by the fact that placebo studies have been carried out in the literature and colonoscopy was successful in from 0 – 15% of patients. Therefore, this combination is clinically effective. Secondly, there are no data presented by the applicant in the pivotal trials regarding the contribution of each component of the Half Lytely — The applicant argues that bisacodyl by itself is not effective, therefore it was not included in the treatment arms of either study. This may be true, however, given

the data presented by the applicant the contribution of each drug component to the efficacy of the HalfLytely — is uncertain, and should not be claimed as known in the label or in promotional announcements.

SAFETY:

Clinical:

The medical reviewer states that the majority of the reported adverse events are non-serious. The majority of events were "expected" as seen with a bowel cleansing system, such as nausea, vomiting, abdominal fullness, and abdominal cramping (for complete details see medial officer review). There were two serious AEs (Hematemesis, rectal bleeding). These AEs resolved spontaneously and were included by the applicant as non-serious.

The safety update was incomplete and submitted very late in the NDA cycle allowing inadequate time for dialogue with the applicant. Omitted from the update are 2 deaths associated with GoLytely in patients with end-stage renal disease, reported in the February BJU, 2003. The same article reported the development of tonic-clinic seizures after administration of GoLytely in a 62-y old female who was on treatment with a diazyde for hypertension. Her serum sodium before colonoscopy was 138 mmol/l and decreased to 116 after colonoscopy. She required intensive care treatment and fully recovered from the serious AE. Two deaths reported in the safety update are of concern.

The Medical reviewer states that the Half Lytely Bowel Prep — shows an acceptable risk benefit. However, the applicant's assessment of the safety data is incomplete. The reports of serious AEs associated with PEG-3350, including death, should be incorporated in the amended label —

F. Labeling Comments:

Draft labeling comments were sent to the applicant June 11, 2003. These were straightforward except for the safety comments. These will need to be discussed further with the applicant. As of June 16, 2003 no responses were received regarding these comments. Therefore, the application is approvable. (see draft labeling attached to the approvable letter)

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/s/

Joyce Korvick
6/16/03 05:23:41 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: June 13, 2003

TO: NDA 21-551

FROM: Alice Kacuba
Regulatory Health Project Manager, HFD-180

SUBJECT: **Memo to file: Financial Disclosure information**
NDA 21-551, Half Lytely® Bowel Prep (PEG-3350 sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets)

The purpose of this memo is outline the financial disclosure information that was reported by the sponsor in NDA 21-551. This is memo is written by request of the Deputy Division Director.

I. Background

A. NDA 21-551 was submitted for the proposed indication of bowel cleansing prior to colonoscopy. In the November 25, 2002 submission, Appendix A contains the financial disclosure information. Appendix A contained the following three items:

1. Form FDA 3454 (06/02) for _____ where Box #1 was checked [As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this firm) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.54(a). I also certify that each listed clinical investigator stating that there were not financial arrangements, propriety interest or significant payments of other sorts as defined in 21 CFR 54(f).]
2. Form FDA 3455 (7/01) for _____ where box 2 was check and the text amended by the sponsor to read: "Any significant payments of other sorts for the duration of the clinical trial _____ from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria."
3. Attachment to Form FDA 3455 for _____ listed the following moneys (significant payments of other sorts) from the years _____ for Braintree _____ and steps taken to minimize potential bias.

Year	Amount Paid (\$)	Description
/	1,000	Honorarium-consulting
	0	--
/	10,000	Consulting
/	10,000	Consulting
/	10,000	Consulting
/		Honorarium-consulting
/	10,000	Consulting
/	3,000	Honorarium-consulting
	2,800	Honorarium to
Total	51,800	

Steps taken to minimize potential bias

1. All trials were minimally single-blinded (investigator was blinded)
2. (preformed)
3. Value of compensation not affected by the outcome of any study

B. According to the firm, _____ was completed in _____ and _____ was completed in _____

C. According to the firm, _____ was completed on _____

III. Regulatory conclusion

A. The moneys paid to _____ as a clinical investigator for _____ are not reportable under the February 2, 1998 Final Rule for Financial Disclosure by Clinical Investigators because the studies were completed prior to the February 2, 1999 effective date.

B. _____ was completed _____ which was completed after the February 2, 1999 effective date. However, _____ was not a clinical investigator for _____. The investigators for _____ are listed on Form FDA 3454.

IV. References

- A. Federal Register notice February 2, 1998; Financial Disclosure by Clinical Investigators
- B. Federal Register notice December 31, 1998; Financial Disclosure by Clinical Investigators
- C. Draft Guidance: Financial Disclosure by Clinical Investigators, March 20, 2001
- D. 21 CFR Part 54
- E. Email consult with ADRA ODE II

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/s/

Alice Kacuba
6/13/03 09:45:34 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 11, 2003

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310

AK

Subject: ~~NDA 21-551~~

Total no. of pages including cover: 10

Comments: Attached is FDA revised labeling. Please note that these are our initial comments on your proposed draft labeling. We have the following attached requested revisions to the labeling (package insert and labels).

Please respond with a written amendment to the NDA, as soon as possible, as well as a fax to my attention. Our major concerns center around the safety section. This is due to the lateness of the submitted Safety Update.

Document to be mailed: YES NO

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9 Page(s) Withheld

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____ § 552(b)(5) Deliberative Process

____ ✓ § 552(b)(5) Draft Labeling



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 6, 2003

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager <i>AK</i>
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310

Subject: ~~NDA 21-551~~

Total no. of pages including cover: *3*

Comments: Attached is an letter regarding NDA 21-551.

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-551
Braintree Laboratories, Inc.
Attention: Vivian Caballero
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Half Lytely (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride and bisacodyl tablets) Bowel Prep

Section 505 of the Act describes three types of new drug applications: 1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); 2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and 3) an application that contains information to show that the proposed product is identical in active ingredients, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j)). You have submitted this application as a 505(b)(1) application. However, because your application relies on the OTC monograph for support of the bisacodyl portion of Half Lytely, we have determined that your application was submitted under 505(b)(2) of the Act. For further information about 505(b)(2) applications, please see the Guidance for Industry: Applications Covered by Section 505(b)(2). The guidance is available at www.fda.gov/cder/guidance/index.htm.

You are required to submit a patent certification for this application according to 21 CFR 315.50(i). Please submit your patent certification as soon as possible.

If you have any questions, call Alice Kacuba, MSN, RN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

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

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/s/

Joyce Korvick
6/5/03 04:44:19 PM
for Dr. Robert Justice



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 30, 2003

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310
Subject: [REDACTED]	

AK

Total no. of pages including cover: 3

Comments: Attached is an Information Request for NDA 21-551. It is urgent that we receive a written response as soon as possible. Please fax me a copy of the submission.

Document to be mailed: YES NO

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I attempted to call to say that the fax was on its way but wasn't disconnected by the receptionist. Please call me if you have questions. I am in a meeting from 3-4:30 PM.
 Alice

To complete the clinical review of NDA 21-551, we are requesting a written response to the following requests:

1. Please provide the cardiology consult report (and any follow-up information) for patient #90 that was treated in Study F38-15 and discontinued because of the AE of an unspecified "cardiac arrhythmia". Specifically, what exact arrhythmia was it.
2. Please provide detailed information on patient exposure to the drug components of the proposed Half Lytely co-therapy (The exposure to both the bisacodyl and to the NuLytely components of the prep kit). If this information has already been submitted, please identify the submission date, volume number, and page number(s).

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/s/

Alice Kacuba
5/30/03 12:13:48 PM
CSO



NDA 21-551

DISCIPLINE REVIEW LETTER

Braintree Laboratories, Inc.
Attention: Vivian Caballero
60 Columbian Street
P.O. Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your August 15, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Half Lytely Bowel Prep (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl tablets).

Our review of the tradename in your submission is complete, and we have the following comments:

We do not recommend use of the proprietary name Half Lytely Bowel Prep. In reviewing the proprietary name "Half Lytely Bowel Prep" the primary concerns raised are related to the potential for "Half" to be misinterpreted as directions for product use as opposed to "Half" being part of the proprietary name, and the packaging configuration of Half Lytely Bowel Prep. In addition, there is a concern that the name may be misleading to practitioners and result in medication errors. Please consider proposing an alternate propriety name.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Alice Kacuba, MSN, RN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Manager Staff
Division of Gastrointestinal and Coagulation Drug Products,
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
5/29/03 04:29:52 PM

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

REQUEST FOR CONSULTATION

○ (Division/Office): Marcie Keister, DDMAC, HFD-042,
Parklawn Building, room 17B-17

FROM: Division of GI and Coagulation Drug
Products (HFD-180)/ Alice Kacuba
(301) 827-7450

DATE May 7, 2003	IND NO. _____	NDA NO. NDA 21-551	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT August 15, 2003
NAME OF DRUG Half-Lytely Bowel Prep		PRIORITY CONSIDERATION _____	CLASSIFICATION OF DRUG Cathartic	DESIRED COMPLETION DATE May 20, 2003 User fee date is June 16, 2003

NAME OF FIRM: Braintree Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

COMMENTS/SPECIAL INSTRUCTIONS:

Background: NDA 21-551 is for Half Lytely Bowel Prep — as a bowel cleansing agent prior to colonoscopy. As mentioned in administrative rounds, this proposed product is 2 liters of the approved Nulytely product and four 5 mg bisacodyl tablets. This is the first review cycle for this NDA. I have just found out that we will be approving the NDA on this first review cycle. I am forwarding you the proposed draft package insert for your review. I will be scheduling some labeling meeting on Outlook. Do you want to be invited to the meetings?

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_____ § 552(b)(5) Draft Labeling

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/s/

Alice Kacuba
5/7/03 04:48:54 PM

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___ § 552(b)(5) Draft Labeling



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 24, 2003

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager <i>AK</i>
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310
Subject: NDA 21-551	

Total no. of pages including cover: 3

Comments: Attached is an Information Request for NDA 21-551.

Document to be mailed: YES NO

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Total 6 pages (2 faxes)

Please submit the following as an amendment to the NDA:

1. Please provide a clarification on serum sodium data for the pivotal studies F38-13/14 and F38-20. If the data is included in the application, please provide the submission date, volume and page number. If the data is not in the present application, please submit this information as soon as possible.

Thank you.

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/s/

Alice Kacuba
4/24/03 04:11:57 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 24, 2003

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager <i>AK</i>
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310
Subject: NDA 21-551	

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Please submit the following marked as a "Review Aid, Not for Archive" to the "Attention of Alice Kacuba, to be opened by addressee only".

1. Please submit an electronic word version of the biopharm section and study summaries.

Thank you.

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/s/

Alice Kacuba
4/24/03 04:17:17 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 22, 2003

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310
Subject: ██████████	

AK

Total no. of pages including cover: 3

Comments: Attached is an Information Request for NDA 21-551.

Document to be mailed: YES NO

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Please submit the following items as an amendment to the NDA:

1. Please submit a Safety Update according to 314.50(d)(5)(vi)(b).

Thank you.

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/s/

Alice Kacuba
4/22/03 06:15:49 PM
CSO

MEMORANDUM OF TELECON

DATE: February 5, 2003

APPLICATION NUMBER: NDA 21-551; Half Lytely Bowel Prep —

BETWEEN:

Name: Ms. Vivian Caballero
Dr. Mark Cleveland
Ms. Carol Polleys
Phone: 781-843-2202
Representing: Braintree Laboratories, Inc.

AND

Name: Ms. Alice Kacuba, Regulatory Health Project Manager
Dr. Wen-Jen Chen, Statistical Reviewer
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Electronic data set for NDA 21-551

BACKGROUND: NDA 21-551 was submitted on August 15, 2002 as a bowel preparation prior colonoscopy examination. On November 25, 2002, the firm submitted an electronic data set. The data set was not submitted in SAS transport files. When Dr. Chen transferred the file set from Excel to SAS, the first row disappeared, making patient number 1 disappear.

Dr. Chen also had additional questions regarding the data set.

TODAY'S PHONE CALL:

1st call

Dr. Chen explained that when he transported the data set into SAS patient number 1 disappeared.

Braintree agreed to submit another data set (electronically and paper). On this set they would leave the top row empty so the same problem would not happen again upon transferring to SAS. Dr. Chen also requested that the firm label each column in text format. Currently each cell is labeled F1, F2, etc. Braintree agreed to make this change.

Dr. Chen asked where the definitions were for ITT and per protocol analysis.

2nd call

Later in the day, Braintree called back regarding our call this morning.

The firm provided the following information regarding your question regarding per protocol analysis and ITT:

For study 13/14, the protocol is described in Volume 1.5 on page 103. The study report in Volume 1.5, page 22 and in Table 6 on page 24 states the primary efficacy analysis. There is also information in Table 6 on page 24.

The per protocol analysis is on page 103, describes both primary efficacy analysis as well as the per protocol analysis. Information is also in Table 5 on page 23 and table 6 on page 24. It sounds like the primary efficacy analysis is ITT.

For study 20, the protocol is on page 314, volume 1.4.2. Study report where efficacy analysis discussed on page 237 and also Table 6 on page 239. The per protocol analysis is in Table 5, page 238.

According to the firm, the efficacy analysis was determined at meetings with the FDA. They attached the meeting minutes on page 201 & page 358.

The firm also pointed out that their November 25, 2002 amendment also speaks to this issue.

3rd call

Dr. Chen I and called Braintree back. It appears that they misunderstood our questions regarding definitions. They provided responses regarding the definitions of the efficacy endpoints. We wanted definitions of the primary and secondary analyses. Braintree agreed that what they were going to use as primary and secondary analyses was not in the protocol.

Braintree did provide the following definitions:

“Per protocol analysis” =everyone that received drug and received colonoscopy.

“ITT” =everyone that received the drug regardless of whethe they received a colonoscopy.

“Super intent to treat” =all enrolled patients.

Braintree will supply these responses in their written response along with the electronic data set.

Alice Kacuba, RN, MSN, RAC
Regulatory Health Project Manager

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/s/

Alice Kacuba
3/5/03 12:55:04 PM
CSO

5 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



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

FACSIMILE TRANSMITTAL SHEET

DATE: October 23, 2002

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310

AK

Subject: [REDACTED]

Total no. of pages including cover: 3

Comments: Attached is an Information Request from chemistry regarding a manufacturing facility for NDA 21-551.

Document to be mailed: YES NO

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Please submit the following items as an amendment to the NDA:

1. For:

1
When the reviewer enters the facility inspection, a different address from what you have provided is listed for this facility. Please clarify the address for

A response to this request is needed by Monday, October 28, 2002.

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/s/

Alice Kacuba
10/23/02 04:39:19 PM
CSO

Alice Kacuba
10/23/02 04:43:36 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: October 21, 2002

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager <i>AK</i>
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7360

Subject: [REDACTED]

Total no. of pages including cover: 3

Comments: Attached is an Information Request from chemistry regarding the manufacturing facilities for NDA 21-551.

Document to be mailed: YES NO

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Please submit the following items as an amendment to the NDA:

1. For:

/

FDA # — , when the reviewer enters the facility inspection, FDA # — shows a different address. Please clarify the address for — FDA #: —

2. For

/

FDA # — when the reviewer enters the facility inspection, FDA # — shows a different address. Please clarify the address for — FDA # —

3. Please provide the FDA # (or also known as CFN number) for the following facilities:

/

A response to this request is needed by Monday, October 28, 2002.

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/s/

Alice Kacuba
10/21/02 05:19:43 PM
CSO



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Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 18, 2002

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310
Subject: ██████████	

AK

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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In addition to the Information Requests that were requested on September 23, 2002, please submit the following items as an amendment to NDA 21-551:

Clinical Information Requests (Response to 1 & 2 should be submitted as soon as possible)

1. Prospective randomization plan for the clinical studies.
2. Clarify how each patient is identified. For example, "Patient 92", is that patient 92 in which study?
3. Provide an intent to treat analysis with all randomized patients
4. Provide an intent to treat analysis with all patients who were given any dose of treatment

Statistical Information Requests

1. Please provide the following information for Study# F38-13/14 and Study# F38-20.
 - a. Please clarify the following issues with regard to the criteria (stated at page 109 of Volume 1.14) used to measure equivalence between two groups on the proportion of successful preparations:
 - i.) Please provide the detail information including the exact formula used to calculate the 90% confidence interval along with its rationale for the equivalence analysis.
 - ii.) Was the delta stated in the paragraph of 90% confidence interval the true (population) difference in proportions of successful preparations? Did you reject the hypothesis of some difference expressed by delta margin to demonstrate the equivalence between two treatments (control group of 4-litter preparation and experiment group of reduced volume preparation)? If you did, please provide the information on the size of delta margin used in the equivalence analysis along with the page and volume numbers where it was stated. If not, please provide exact formula for your equivalence analysis.
 - iii.) Please provide the references if particular journal articles were used for your equivalence analysis or the justifications.
 - b. The sample size calculations presented at page 108 of Volume 1.14 is not clear. It is difficult to know how the sample size was calculated: based on one tailed test or equivalence analysis. In order to clarify the above question, please provide the detail information including the exact formula used to calculate the sample size along with the justifications in support of the sample size calculation.
 - c. As to the ridit analysis, the definition of the reference group at page 18 of Volume 1.14 was not clear. Was the reference group consisted of all patients from the two groups (control group of 4-litter preparation and experiment group of reduced volume preparation) or just from experiment group? Please use Table 5 presented at page 23 of Volume 1.14 as an example to demonstrate (step by step) how you calculated the mean Ridit for 2L+bis (experiment) group. In addition, please also provide the references of journal articles or justifications for the standard error of the mean ridit (r) proposed at page 18 of Volume 1.14.

d. Please provide the definition of ITT (Intent-to-Treat) population used in your studies. Was the primary analysis based on ITT population? If not, please indicate what population, along with the definition, the primary analysis was based upon.

2) Please provide data for both Studies F38-13/14 and F38-20 in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations*. It is suggested that the following variables be included:

Study number;
Investigator or Center code;
Patient number/name;
Treatment name;
Intent-to-treat population (Yes or No);
Protocol population (patients complied with the protocol) (Yes or No);
Patient used in the primary analysis (Yes or No);
Patient used in the secondary analysis (Yes or No);
Gender ;
Age (year);
Race;
Weight (kg);
Bowel cleansing quality scored by the colonoscopist on a four point scale (poor to excellent);
Bowel preparation rating (successful or unsuccessful);
Clinical adequate assessment on bowel preparations (adequate or inadequate);
Symptom of fullness assessed by patients using a five point scale: (none to severely);
Symptom of cramping assessed by patients using a five point scale (none to severely);
Symptom of Nausea assessed by patients using a five point scale (none to severely);
Symptom of vomiting assessed by patients using a five point scale (none to severely);
Symptom of discomfort assessed by patients using a five point scale (none to severely).

Please provide interpretation for each submitted variable name.

3) Please provide programs applied Redit analysis, stated in the section of Data analysis at page 17 of Volume 1.14, to the physician's scores on the bowel cleansing quality and the patient's scores on the symptoms of fullness, cramps, nausea, vomiting, and discomfort for both Studies F38-13/14 and F38-20. To the data set described by 2), please add any additional variables needed for these Redit analyses.

Biopharm Information Requests

1. Please address the potential drug-drug interaction (DDI) between bisacodyl and PEG 3350.

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/s/

Alice Kacuba
10/18/02 06:35:21 PM
CSO

filing minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 2, 2002

Time:

Location: Parklawn Building, 6B-45

Application: NDA 21-551; Half Lytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride and bisacodyl tablets) Bowel Prep —

Type of Meeting: 45 Day Filing Meeting

Meeting Chair: Hugo Gallo-Torres

Meeting Recorder: Alice Kacuba

FDA Attendees, Titles, and Office/Division:

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

Robert Justice; Division Director
Joyce Korvick; Deputy Division Director
Hugo Gallo-Torres; Medical Team Leader, GI
Robert Prioznt; Medical Reviewer
Liang Zhou; Chemistry Team Leader
Jasti Choudary; Pharmacology Team Leader
Tamal Chakraborti; Pharmacology Reviewer

Division of Pharmaceutical Evaluation II (HFD-870)

Albert Chen; Biopharmaceutics Reviewer

Division of Biometrics III (HFD-720)

Tom Permutt; Statistical Team Leader
Wen-Jen Chen; Statistical Reviewer

Background: Braintree Laboratories, Inc. submitted NDA 21-551 on August 15, 2002 (received August 16, 2002) for Half-Lytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets) Bowel Prep — for the proposed indication of bowel cleansing prior to colonoscopy. This product consists of 4 (5 mg) bisacodyl tablets and a jug of 2 Liters of Nulytely for oral solution.

— The bisacodyl tablets are to be administered first. Upon having the first bowel movement or 6 hours later, the patient is to drink the 2 Liters Nulytely (reconstituted) at a rate of 240 mL every ten minutes.

The filing date for this application is October 15, 2002.

Meeting Objective:

To determine the fileability of this application.

Discussion Points (bullet format):

I. Administrative

- A. Filing Issues: None (See RPM administrative review dated September 23, 2002).
- B. Information Requests:
 - (i) The following was requested in a September 20, 2002 phone call: a revised table to include the number of patients enrolled per site to facilitate the selection of clinical sites for possible audit.
 - (ii) The following items were requested in a September 23, 2002 fax to the firm:
 - Three desk copies of Volume 1.1
 - One desk copy of the volume which contains the ISS and ISE
 - Financial disclosure information
 - An electronic copy of the labeling (package insert and labels) on diskette in MS WORD
 - One of the three options under 21 CFR 314.55 for pediatric data
 - An electronic copy of the Biopharmaceutical information and study summaries in MS WORD
 - Patent information per 21 CFR 314.53
- C. Other Issues: None

II. Clinical

- A. Filing Issues: None
- B. Information Requests:
 - i. Prospective randomization plan for the clinical studies.
 - ii. Clarify how each patient is identified. For example, "Patient 92", is that patient 92 in which study?
 - iii. Provide an intent to treat analysis with all randomized patients.
 - iv. Provide an intent to treat analysis with all patients who were given any dose of treatment.
- C. DSI audits: To be determined. DSI audit request to be sent by November 1, 2002.
- D. Other Issues: None

III. Statistical

- A. Filing Issues: None
- B. Information Requests:

1. Please provide the following information for Study# F38-13/14 and Study# F38-20.
 - a. Please clarify the following issues with regard to the criteria (stated at page 109 of Volume 1.14) used to measure equivalence between two groups on the proportion of successful preparations:
 - i.) Please provide the detail information including the exact formula used to calculate the 90% confidence interval along with its rationale for the equivalence analysis.
 - ii.) Was the delta stated in the paragraph of 90% confidence interval the true (population) difference in proportions of successful preparations? Did you reject the hypothesis of some difference expressed by delta margin to demonstrate the equivalence between two treatments (control group of 4-litter preparation and experiment group of reduced volume preparation)? If you did, please provide the information on the size of delta margin used in the equivalence analysis along with the page and volume numbers where it was stated. If not, please provide exact formula for your equivalence analysis.
 - iii.) Please provide the references if particular journal articles were used for your equivalence analysis or the justifications.
 - b. The sample size calculations presented at page 108 of Volume 1.14 are not clear. It is difficult to know how the sample size was calculated: based on one tailed test or equivalence analysis. In order to clarify the above question, please provide the detail information including the exact formula used to calculate the sample size along with the justifications in support of the sample size calculation.
 - c. As to the ridit analysis, the definition of the reference group at page 18 of Volume 1.14 was not clear. Was the reference group consisted of all patients from the two groups (control group of 4-litter preparation and experiment group of reduced volume preparation) or just from experiment group? Please use Table 5 presented at page 23 of Volume 1.14 as an example to demonstrate (step by step) how you calculated the mean Ridit for 2L+bis (experiment) group. In addition, please also provide the references of journal articles or justifications for the standard error of the mean ridit (r) proposed at page 18 of Volume 1.14.
 - d. Please provide the definition of ITT (Intent-to-Treat) population used in your studies. Was the primary analysis based on ITT population? If not, please indicate what population, along with the definition, the primary analysis was based upon.

- 2) Please provide data for both Studies F38-13/14 and F38-20 in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations*. It is suggested that the following variables be included:

Study number;
Investigator or Center code;
Patient number/name;
Treatment name;
Intent-to-treat population (Yes or No);
Protocol population (patients complied with the protocol) (Yes or No);
Patient used in the primary analysis (Yes or No);
Patient used in the secondary analysis (Yes or No);
Gender ;
Age (year);
Race;
Weight (kg);
Bowel cleansing quality scored by the colonoscopist on a four point scale (poor to excellent);
Bowel preparation rating (successful or unsuccessful);
Clinical adequate assessment on bowel preparations (adequate or inadequate);
Symptom of fullness assessed by patients using a five point scale: (none to severely);
Symptom of cramping assessed by patients using a five point scale (none to severely);
Symptom of Nausea assessed by patients using a five point scale (none to severely);
Symptom of vomiting assessed by patients using a five point scale (none to severely);
Symptom of discomfort assessed by patients using a five point scale (none to severely).

Please provide interpretation for each submitted variable name.

- 3) Please provide programs applied Rudit analysis, stated in the section of Data analysis at page 17 of Volume 1.14, to the physician's scores on the bowel cleansing quality and the patient's scores on the symptoms of fullness, cramps, nausea, vomiting, and discomfort for both Studies F38-13/14 and F38-20. To the data set described by 2), please add any additional variables needed for these Rudit analyses.

C. Other issues: None

IV. Chemistry, Manufacturing and Controls

- A. Filing Issues: None
B. Information Requests: None at this time
C. Other Issues:
i. The EER has been sent
ii. The tradename consult has been sent

- iii. A consult to Dan Boring (Nomenclature) and Mille Yana has been sent to evaluate the "Bowel Prep" language in the proposed name

V. Biopharmaceutics

- A. Filing Issues: None
B. Information Requests: Please address the potential drug-drug interaction (DDI) between bisacodyl and PEG 3350.
C. Other Issues: None

Conclusions:

1. It was agreed that the application would be filed.
2. An Information Request (IR) letter has been sent to the firm requesting the information requests.
3. This application has a 10 month User Fee Goal Date of June 16, 2003.
4. The following goal dates were set (See Appendix I for Timeline):
 - June 16, 2003 = action goal date
 - May 16, 2003 = completed action package to the Division Director or Deputy Division Director
 - April 16, 2003 = Divisional goal date (all reviews are to be finalized in DFS by this date)

Minutes Preparer:

Chair Concurrence:

DFS

cc: Original NDA 21-551

HFD-180/A.Kacuba

HFD-180/R.Justice

HFD-180/Korvick

HFD-180/H.Gallo-Torres

HFD-180/R.Prizont

HFD-180/L.Zhou

HFD-180/M.Ysern

HFD-180/J.Choudary

HFD-180/T.Chakraborti

HFD-870/S.Doddapaneni

HFD-870/A.Chen

HFD-720T.Permutt

HFD-720/W.Chen

Drafted by: A.Kacuba/October 2, 2002

Initialed by: H.Gallo-Torres/October 22, 2002

Final: AK/October 22, 2002

Filename: c:\wpfiles\21551\filng-meeting-minutes.doc

MEETING MINUTES

Appendix 1

NDA 21-551

Half Lytely® (PEG =-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets) Bowel Prep —

Indication: Bowel cleansing prior to colonoscopy

Reviewers:

Clinical= Robert Prizont

CMC= Maria Ysern

Stats= Wen-Jen Chen

Biopharm= Albert Chen

Pharm/tox= Tamal Chakraborti

Signoff= Division Director/Deputy Division Director

VI. Action item	VII. Action Date
Letter date	August 15, 2002
Stamp date	August 16, 2002
Filing meeting	October 2, 2002
Filing date	October 15, 2002
Month 5 team meeting	TBS
Month 7 team meeting	TBS
Divisional Goal Date (all reviews finalized in DFS)	May 16, 2003
Action package to DD/DDD	May 27, 2003
Labeling meeting #1 (if needed)	TBS
Labeling meeting #2 (if needed)	TBS
Labeling meeting #3 (if needed)	TBS
10 month user fee date	June 16, 2003

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/s/

Alice Kacuba
10/22/02 04:07:50 PM

Hugo Gallo Torres
10/24/02 06:55:20 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-551

Braintree Laboratories, Inc.
Attention: Vivian A. Caballero
Director, Regulatory Affairs
60 Columbian Street West
P.O. Box 850929
Braintree, MA 02185-0929

Dear Ms. Caballero:

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

Name of Drug Product: Half Lytely[®] (peg-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets) Bowel Prep

Review Priority Classification: Standard (S)

Date of Application: August 15, 2002

Date of Receipt: August 16, 2020

Our Reference Number: NDA 21-551

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 15, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 16, 2003.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, R.N., MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Alice Kacuba
9/24/02 11:58:51 AM



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

FACSIMILE TRANSMITTAL SHEET

DATE: September 23, 2002

To: Vivian Caballero	From: Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager
Company: Braintree Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 781-843-7932	Fax number: 301-443-9285
Phone number: 781-843-2202	Phone number: (301) 827-1602 or 7310
Subject: NDA 21-551	

Total no. of pages including cover: 2

Comments: An acknowledgement letter for your NDA for Half Lytely Bowel Prep will be forthcoming. NDA 21-551 has been assigned to this NDA.

Attached is a list of Information Requests for NDA 21-551. Please note that a further request will be forthcoming regarding the submission of the efficacy data in electronic format. After our internal filing meeting, there may be further Information Requests.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-1602. Thank you.

Please submit the following items as an amendment to the NDA:

1. Three desk copies of Volume 1.1
2. One desk copy of the volume which contains the ISS and ISE
3. Financial disclosure information
4. An electronic copy of the labeling (package insert and labels) on diskette in MS WORD
5. One of the three options under 21 CFR 314.55 for pediatric data
6. An electronic copy of the Biopharmaceutical information and study summaries in MS WORD
7. Patent information per 21 CFR 314.53

If any of these requests are currently in the NDA, please provide a volume and page number.
If you feel any of these requests are not necessary, please include that as part of your response.

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/s/

Alice Kacuba
9/23/02 06:59:13 PM
CSO

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-551

Name of Drug: Half Lytely® (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets) Bowel Prep —

Sponsor: Braintree Laboratories, Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Paper

Submission Date: August 15, 2002

Receipt Date: August 16, 2002

Filing Date: October 15, 2002

User-fee Goal Date: 10 month date = May 16, 2003

Proposed Indication: For bowel cleansing prior to colonoscopy

Other Background Information:

This proposed indication was discussed in meetings between the Agency and Braintree on June 9, 1993 and on October 5, 1998. An Advice letter was also sent to Braintree on February 17, 1999, subsequent to 57,673 submission.

Review

PART I: OVERALL FORMATTING^{a,d,e}

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Volume 1.1, page not numbered
2. Form FDA 356h (original signature)	X		Volume 1.1, page not numbered
a. Establishment information	X		Volume 1.1, page not numbered

b. Reference to DMF(s) & Other Applications	X	Volume 1.1, on 356h form IND 28,741, IND 57,673 DMF
3. User Fee FDA Form 3397	X	Volume 1.1, page not numbered
4. Patent information & certification	X	<i>Requested</i>
5. Debarment certification (Note: Must have a definitive statement)	X	Volume 1.1, page not numbered
6. Field Copy Certification	X	Volume 1.1, page not numbered
7. Financial Disclosure	X	The firm should be requested to submit this per 21 CFR 314.50(k).
8. Comprehensive Index	X	Volume 1.1
9. Pagination		Volume 1.1 is not numbered. However it is sufficiently divided by tabs.
10. Summary Volume	X	Volume 1.1
11. Review Volumes	X	
12. Labeling (PI, container, & carton labels)		
a. unannotated PI	X	Volume 1.1
b. annotated PI	X	Volume 1.1
c. immediate container	X	Volume 1.1
d. carton	X	
e. patient package insert (PPI)	X	N/A
f. foreign labeling (English translation)	X	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X	Volume 1.8-1.11
14. Case Report Forms (paper or electronic) (for death & dropouts due	X	Volume 1.12

to adverse events)			
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Y=Yes (Present), N=No (Absent)

PART II: SUMMARY^{b,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Volume 1.1, Summary tab, page 6
2. Foreign Marketing History	X		Volume 1.1, Summary tab, page 10
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 1.1, Summary tab, page 10
b. Nonclinical Pharmacology/Toxicology	X		Volume 1.1, Summary tab, page 10
c. Human Pharmacokinetic & Bioavailability			Volume 1.1, Summary tab, page 20
d. Microbiology		X	N/A
e. Clinical Data & Results of Statistical Analysis	X		Volume 1.1, Summary tab, page 36
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies		X	
5. Summary of Safety	X		Volume 1.7, page 27
6. Summary of Efficacy	X		Volume 1.7, page 36

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

PART III: CLINICAL/STATISTICAL SECTIONS^{c,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)

1. List of Investigators	X		Volume 1.4, page i-1 and Volume 1.13, page 1
2. Controlled Clinical Studies			
a. Table of all studies			Volume 1.4 page ii-1
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Volume 1.4
c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)	X		Volume 4.4 page 28-36
4. Integrated Summary of Safety (ISS)	X		Volume 4.4 page 37-100
5. Drug Abuse & Overdosage Information	X		Volume 1.7, page 150
6. Integrated Summary of Benefits & Risks of the Drug		X	
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	X		In ISE and ISS

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

PART IV: MISCELLANEOUS^{d,e}

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	The firm should be requested to submit this information per 21 CFR 314.55.

2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			
a. Proposed unannotated labeling in MS WORD		X	The firm should be requested to submit the draft labeling on diskette in WORD.
b. Stability data in SAS data set format (only if paper submission)		X	CMC will need to determine if this is necessary.
c. Efficacy data in SAS data set format (only if paper submission)		X	At the filing meeting, the statistical reviewer should identify what review aids are needed.
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	The firm should be requested to submit this.
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	Pharm/tox will need to determine if this is necessary.
3. Exclusivity Statement (optional)		X	

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

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

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

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

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

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

Additional Comments:

The filing meeting for this application is scheduled for October 2, 2002.

On September 20, 2002, the firm has been asked to submit a revised table of investigators listing how many patients were enrolled per center. The firm has agreed to submit a revised table. The revised table will be used to assist the Medical Officer in determining what, if any, clinical sites will require a DSI audit.

Conclusions:

The NDA is fileable from the administrative perspective. However, the firm should be requested to submit the following items as an amendment to the NDA:

1. Three desk copies of Volume 1.1
2. One desk copy of the volume which contains the ISS and ISE
3. Financial disclosure information
4. An electronic copy of the labeling (package insert and labels) on diskette in MS WORD
5. One of the three options under 21 CFR 314.55 for pediatric data
6. An electronic copy of the Biopharmaceutical information and study summaries in MS WORD
7. Patent information per 21 CFR 314.53

Name
Regulatory Project Manager

ADMINISTRATIVE REVIEW

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/s/

Alice Kacuba
9/23/02 06:37:16 PM
CSO

REQUEST FOR CONSULTATION

TO (Division/Office):

1). Dan Boring, HFD-530, Corporate Building, Room S447
2). Yana Mille, HFD-354, Room 3072, WOC2,

FROM: Liang Zhou, Chemistry Team leader,
Maria Ysem, Chemistry Reviewer
Alice Kacuba, Regulatory Health Project Manager
HFD-180

DATE October 11, 2002	IND NO.	NDA NO. 21-551	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT August 15, 2002
NAME OF DRUG Half Lytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride and bisacodyl tablets) Bowel Prep		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Cathartic	DESIRED COMPLETION DATE April 1, 2003

NAME OF FIRM: Braintree Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NOA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | XXXX OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

COMMENTS/SPECIAL INSTRUCTIONS: Braintree Laboratories, Inc, has submitted an NDA for Half Lytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride and bisacodyl tablets) Bowel Prep — which is 4 (5 mg) bisacodyl tablets and 2 liter of Nulytely fore the indication of bowel cleansing prior to colonoscopy.

We have sent a tradename consult to DMETS to evaluate the proposed tradename and that consult review is pending. In our internal discussions at our recent filing meeting, we discussed the terminology of the proposed dosage form of "Bowel Prep — . In an attempt to avoid any last minute review issues, we want to consult you on the acceptability of the terminology of "Bowel Prep —

The chemistry reviewer is Maria Ysem. Maria can be reached at 7-7468. Liang Zhou is the team leader and can be reached at 7-7471.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Alice Kacuba

10/11/02 04:23:43 PM

The hardcopy of the consult will contain the proposed
lableing

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

APPLICANT'S NAME AND ADDRESS

RAINTREE LABORATORIES, INC.
Columbian Street West
P.O. Box 850929
Raintree, MA 02185

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 21-551

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

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

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

TELEPHONE NUMBER (Include Area Code)

781) 843-2202

PRODUCT NAME

LyteLy

6. USER FEE I.D. NUMBER
4404

IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY
(Self Explanatory)

A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See item 8, reverse side if answered YES)

The reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Washington, DC, HFM-99
Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE

Director, Regulatory Affairs

8/15/2002

DA 3397 (4/01)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
(Division/Office): Associate Director, Medication Error Prevention Office of Drug Safety, HFD-400 (Sammie Beam-Rm. 6-34, PKLN Bldg.)		FROM: Alice Kacuba, Regulatory Health Project Manager, HFD-180		
DATE Sept 20, 2002	IND NO.	NDA NO. 21-551	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT August 15, 2002
NAME OF DRUG Half Lytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride and bisacodyl tablets) Bowel Prep	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Cathartic	DESIRED COMPLETION DATE April 15, 2003	
NAME OF FIRM: Braintree Laboratories, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review <input type="checkbox"/> MEETING PLANNED BY				
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Braintree has submitted a NDA for Half Lytely Bowel Prep as a bowel cleansing agent prior to colonoscopy. The 10 month goal date for this NDA is June 16, 2003, with a Divisional Goal date for completed divisional reviews by May 15, 2003. Please complete the tradename review by April 15, 2003 in order for the reviewers to complete their reviews by the Division goal date. Thank you.				
Please note that this version of the consult supercedes the consult request dated September 19, 2002, which contained incorrect due dates. Please call me if there is any confusion regarding the due dates of this consult. Thank you.				
PDUFA DATE: June 16, 2003 ATTACHMENTS: Draft Package Insert and Container Labels				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Alice Kacuba
9/20/02 09:58:13 AM



IND 57,673

Food and Drug Administration
Rockville MD 20857

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

FEB 17 1999

Dear Dr. Cleveland:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for ½ LYTELY Bowel Prep — (bisacodyl 20 mg tablets and 2 liters of NuLYTELY powder for oral solution).

We have completed the clinical review of your submission, and have the following comments and recommendations regarding protocol F38-20, entitled, "½ NuLYTELY Bowel Prep System for Colonoscopy." In this study, 200 patients will be randomized to either 4 liters NuLYTELY or to 20 mg bisacodyl tablets followed by 2 liters NuLYTELY (2L+bis).

1. Extrapolating efficacy from one product to another across clinical trials, particularly those based on data suggesting equivalence, is not an acceptable approach. We recommend that the proposed study be redesigned to compare: 2L+bis, 20 mg bisacodyl alone, 2 liters of NuLYTELY alone, and the standard 4 liters of NuLYTELY. The study needs to be sized to demonstrate equivalence of ½ LYTELY and NuLYTELY and superiority of ½ LYTELY and NuLYTELY to each 20 mg bisacodyl and 2 liters NuLYTELY.
2. Please list "routinely accepted indications" for which colonoscopy is to be done. The indication for colonoscopy should be recorded for each patient enrolled. *ICFA list.*
3. Please provide a list of concomitant medications that are not allowed during the study, (e.g., non-study laxatives, antacids, gastrointestinal motility-modifying drugs such as metoclopramide and cisapride).
4. Please consider excluding patients with certain diseases (e.g., active inflammatory bowel disease, uncontrolled cardiovascular disease).
5. To decrease the potential for bias, you should arrange for study personnel who are not involved in performing the colonoscopy to collect and review with the patients the questionnaires for compliance (pill counts, volume of remaining solution) and adverse events.

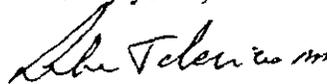
6. Analysis of the data may be complicated by the fact that if patients ingest solution only until "the rectal effluent runs clear," the actual amount of solution ingested is likely to vary from patient to patient making it difficult to distinguish between patients who are non-compliant and those who achieve a clear rectal effluent with intake of less than the total amount of the solution. Please address this concern.
7. We recommend addressing the use of ½ LYTELY in elderly patients, as there is a potentially greater risk to elderly patients with regard to electrolyte imbalance and dehydration, as well as for poor preparation result with bowel preparation regimens.
8. We also request that you describe plans for pediatric development.

We hope that this information is helpful.

If you have any questions, please contact:

Alice Kacuba
Consumer Safety Officer
(301) 827-7310

Sincerely yours,



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

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 5, 1998
Time: 10:00-11:30 AM
Location: Parklawn Building, Conference Room "P"

Application: ½ LYTELY Bowel Prep

Type of Meeting: Pre-NDA Meeting

Meeting Chair: Dr. Lilia Talarico

Meeting Recorder: Ms. Alice Kacuba

FDA Attendees, Titles, and Office/Division:**Division of Gastrointestinal and Coagulation Drug Products (HFD-18)**

Dr. Lilia Talarico; Division Director
Dr. Hugo Gallo-Torres; Medical Team Leader
Dr. Jasti Choudary; Pharmacology Team Leader
Dr. Eric Duffy; Chemistry Team Leader
Dr. Ray Frankewich; Chemistry Reviewer
Ms. Kati Johnson, SCSO
Ms. Alice Kacuba, CSO

Division of Pharmaceutical Evaluation II (HFD-870)

Mr. John Hunt; Deputy Director

Division of Biometrics III (HFD-720)

Dr. Abdul Sankoh; Statistical Team Leader

External Constituent Attendees and Titles:**Braintree Laboratories, Inc.**

Dr. Mark Cleveland; Vice President, New Product Development

Dr. Wayne Pierson; Statistician

Ms. Vivian Caballero; Director of Regulatory Affairs

Background: Braintree Laboratories plans to submit an application for ½ LYTELY Bowel Prep as a purgative agent for colonoscopy. ½ LYTELY is the firm's proposed trade name for a

combination product consisting of bisacodyl 20 mg (4 X 5 mg tablets) and a reduced volume (2 Liters upon reconstitution) of NuLYTELY powder. NuLYTELY (a mixture of PEG and Electrolytes) is currently marketed (under NDA 19-797) as a powder reconstituted to 4 Liters and administered prior to a colonoscopy. The firm has requested a meeting to discuss clinical, chemistry, manufacturing and controls, and pharmacology and toxicology issues.

In the September 11, 1998 background package, the firm described the single study planned for inclusion in their future submission. Protocol F38-13/14 enrolled 200 patients in two study centers and compared the 2L + bis preparation to 4L of NuLYTELY for adequacy of bowel cleansing prior to colonoscopy. According to the firm, the primary efficacy endpoint of "successful" vs. "unsuccessful" bowel cleansing (an intent-to-treat analysis) demonstrated that the two preparations produced equivalent results.

In a secondary measure, subjective physician rating of "clinical adequacy" of preparation, the 2L + bis had a slightly poorer rating than the 4L prep, a result the firm attributed to an unusually favorable rating for the 4L preparation in this study relative to that observed historically.

Meeting Objectives:

1. To address the questions identified in the September 11, 1998 background package.

Discussion Points:

In response to the firm's questions, the following agreements were reached after discussion. The format provides the firm's questions, followed by the Agency's responses in bolded lettering.

General and Labeling

1. This project was originally positioned as a supplement to the NuLYTELY NDA (19-797). Since we do not intend to discontinue the 4L NuLYTELY preparation, how should this application be submitted?
 - **It should be submitted as an NDA.**
2. Concerning the regulatory status of bisacodyl; does the proposed change of bisacodyl from Category I to Category III (Federal Register June 19, 1998) effect this single use application and how should it be addressed?
 - **The labeling will include information about the regulatory status of bisacodyl**
 - **How do you plan to address the issue that the regulatory status of bisacodyl is based on a 10-15 mg dose?**

-Since 20 mg is the dose that is used in the bowel cleansing system identified in the OTC monograph, it was determined that the firm's proposed dose was no longer an issue.

3. Please comment on the proposed labeling (see pages 4 - 11 of Supporting Documentation).
 - **Labeling can only be addressed during a comprehensive review of the application.**
4. The generic name for ½ LYTELY Bowel Prep is "PEG 3350, Sodium Chloride, Sodium Bicarbonate, Potassium Chloride for Oral Solution and Bisacodyl Tablets". Is this acceptable?
 - **This will be determined during the review process.**

Clinical

1. One pivotal study performed at two study centers (Braintree Protocol F38-13/14) with supporting studies from the published literature will be supplied to demonstrate the efficacy and safety of the 2L+bis product. Will this be sufficient for approval?
 - **Approvability of an application can only be determined after completion of a comprehensive review of the submitted data.**
 - **The acceptance of a single study requires :**
 - large multicenter study with consistency across centers
 - consistency across subsets
 - statistically persuasive finding

Based on the available data in the background package, the results do not look compelling.

- **We recommend that you consider conducting another large multicenter study using the bisacodyl formulation planned for market with the primary endpoint of adequacy of preparation for colonoscopy. We also suggest that efficacy be evaluated as a binary outcome; success vs. failure. We also recommend that the need for re-preparation be evaluated.**
- **The Agency offered to review any proposed protocol prior to study initiation.**

2. *Braintree Protocol F38-13/14*

The firm has concluded that (based on results from study F38-13/14) that the 2L+bis preparation is equivalent in terms of cleansing efficacy to the 4L preparation with a large reduction in preparation related side effects. The F38-13/14 study is sufficient and adequate to provide evidence for a conclusion of efficacy and safety for approval of the 2L+bis preparation. Do you agree?

- It is premature for us to conclude anything prior to a comprehensive review of the data.

3. *Published Studies*

Additional supporting information will consist of several published reports which studied bisacodyl in combination with reduced volumes of GoLYTELY for bowel preparation following closely similar regimens to 2L+bis (for example see Adams et al and Sharma et al in Appendix B of Supporting Documentation). Since NuLYTELY and GoLYTELY have been determined to be equivalent, these studies are sufficient and adequate to provide information in support of a conclusion of safety and efficacy for the 2L+bis preparation. Do you agree?

- NuLYTELY was approved based on the demonstration of equivalence to GoLYTELY. Therefore, it would be appropriate to cite these articles as supporting information. Provide the articles, as well as a summary of the articles. However, it is impossible for us to draw meaningful conclusions prior to a comprehensive review of the data.

-The firm inquired, if they were able to obtain the source documentation for the published studies that they reference, could this substitute for conducting another study?

- Since these studies did not use Nulytely, they would not be a substitute for conducting another study.

4. *Braintree Protocol F38-15*

This study was undertaken to meet the regulatory requirements for a combination drug product. The study compared bowel preparation for colonoscopy using 20mg bisacodyl alone, or 2L of NuLYTELY alone, to the approved 4L NuLYTELY preparation (see pages 23 to 29 in "Supporting Documentation"). The study demonstrated that preparation with either component alone was inferior to preparation with 4L NuLYTELY. This study is adequate to meet the requirements for a combination drug product for the 2L+bis preparation. Do you agree?

- Based on available data, the design of study F38-15 appears adequate to evaluate the contribution of each component to the claimed effect as required by 21 CFR 300.50. The adequacy of the study can only be determined following a comprehensive review of the submitted data.

Pharmacology/Toxicology

1. With respect to the NuLYTELY component of the 2L+bis product, it is our intention to cross reference NDA 19-797 (NuLYTELY). Is any other information required?
- To facilitate the review, we would prefer that you resubmit the NuLYTELY information and certify that it is identical to what was originally submitted. A summary of the information would also be helpful.

2. With respect to the bisacodyl component (a well established OTC laxative) of the 2L+bis product, we intend to reference the January 25, 1985 Federal Register notice that bisacodyl is a Category I OTC Laxative (as described on pages 22-23 of Supporting Documentation). Is other information required?
 - Please provide copies of any relevant literature and a summary of that literature. Your intended reference to the Federal Register notice should be more recent.
3. For the 2L+bis combination product (consisting of 20 mg bisacodyl followed 4-6 hours later by 2L NuLYTELY), published literature as well as the blood analyte results of the pivotal clinical study will be referenced (as discussed at the June 9, 1993 meeting between Braintree and FDA, see Appendix A of Supporting Documentation). The published literature information will include two studies which show that bisacodyl does not promote PEG absorption in rats (see Appendix B of Supporting Documentation, Saunders et al, for one such study). In addition, the pivotal clinical study (F38-13/14) included measurements of serum analytes which showed no clinically significant differences between the 2L+bis prep and the approved 4L prep. Is other information required?
 - No

Chemistry

1. This application will include manufacturing and stability information for three 2L+bis variants. These will be 20 mg bisacodyl with unflavored 2L NuLYTELY; 20mg bisacodyl with cherry 2L NuLYTELY; and 20mg bisacodyl with lemon-lime 2L NuLYTELY. How should this information be organized in the application?
 - Provide stability data on the market package for the 20 mg tablet and 2 Liter NuLYTELY for each flavor.
 - Provide the following information for the lemon-lime flavoring:
 - chemical composition
 - source, DMF number, and LOA
 - gas production studies, to demonstrate whether potentially explosive gas is produced when flavoring is metabolized.
 - Provide the following information for the container closure system:
 - manufacturer
 - chemical composition
 - source, DMF number, and LOA

2. The stability of NuLYTELY and bisacodyl are well established. Therefore, in the application we intend to submit stability testing data from accelerated conditions to — for both components. For room temperature data (25°C) data to — storage will be supplied for the 2L NuLYTELY component and data to — storage for the bisacodyl component will be submitted with the application. Additional stability data will be supplied during application review. Is this acceptable?
 - We can not commit to reviewing any additional data submitted after the filing date.
 - We recommend submitting the data specified in ICH Q1A (12 months real time data, 6 months accelerated data).
3. Are there any specific requirements for attachment of the bisacodyl tablets to the 2L container?
 - There are no specific requirements.
4. For the NuLYTELY component, raw material and in-process — testing will be done according to the approved NuLYTELY application procedures. Is cross referencing to the NDA acceptable? How should this be done?
 - This is acceptable only if the cross referenced information is identical to that proposed for this application.
 - When referencing the NDA, supplements, or annual reports, provide the date of submission, volume numbers and page numbers. Alternatively, to expedite the review process, resubmit the data in this application.
5. In conformance with the USP specifications for a similar product (PEG 3350 and Electrolytes for Oral Solution), finished product specifications for the NuLYTELY component PEG and salt ingredients will be + — Is this acceptable?
 - It appears to be acceptable.
6. Analytical testing for bisacodyl tablets will be performed according to USP 23 for the incoming, packaged bisacodyl tablets. No additional analytical testing of the bisacodyl component will be performed prior to the 2L+bis product release, however, visual inspection for correctness and tablet count will be performed. Is this acceptable?
 - The firm was requested to address the following in the application:
 - Sampling:**
 - How will the incoming product be sampled for testing?
 - Specifically:**
 - How large will each incoming shipment of bisacodyl tablets be?

- How many units per batch will be sampled?
 - If shipment size/sample size varies, is there a statistical procedure involved in determining the number of samples? If so, describe the procedure. If no statistical procedure is involved, then give a complete description of what process is used and the specific logic on which it was based.
 - In general, ensure that representative sampling is obtained.
7. The bisacodyl tablets will be obtained as bisacodyl tablets, USP from an approved supplier. What drug substance and manufacturing information relative to the bisacodyl tablets will be required in the application?
- Reference the NDA/ANDA and provide an LOA from the sponsor(s) of those applications.
 - Provide information on the drug's solubility as a function of pH and dissolution data using a medium that might allow for drug dissolution; for example, surfactants that might mimic the effects of the bile salts.
 - Drug product - will need a DMF which has master batch records, acceptance tests and specifications, release tests and specifications, and change controls.
 - Drug substance - will need information on drug substance.
 - Expiry - The expiry period begins when the active ingredient is introduced into the manufacturing process. The combination product will have a single expiry date.

Other Comments

- Clarify the product(s) used in the clinical study and if possible, the supportive studies, as well as the product that is to be marketed. Once this information is determined and assessed, it was recommended that a telecon might be appropriate to address any biopharmaceutics concerns.
- For bisacodyl, you have indicated in your proposed package insert that "Bisacodyl is poorly absorbed, if at all, in the small intestine following oral administration, nor in the large intestine following rectal administration. Also, there is information that bisacodyl is eliminated via the renal route of elimination. Please provide the information and data related to these claims/findings (e.g., literature, etc.). A copy of a publication was provided to the firm that demonstrated bisacodyl's systemic exposure from a solution and oral tablet.
- Assess whether there is information available on the metabolism of bisacodyl.
- It was requested that the information to support the proposed _____ needed to be provided.
- It was noted that 21 CFR 320 needed to be addressed; either submitting bioavailability/bioequivalence data or a waiver of not needing to submit bioavailability/bioequivalence data.

- State that the manufacturing facilities are ready for inspection.
- Clearly state what each facility does.

Minutes Preparer: Alii Kacuda 11-5-98

Chair Concurrence: Rob Teleno 11-5-98

cc: Original

HFD-/Div. Files

HFD-/Meeting Minutes files

HFD-/CSO/A.Kacuba

HFD-/reviewers & attendees

Drafted by: A.Kacuba/October 18, 1998

Initialed by: K.Johnson/October 22, 1998/Novemeber 5, 1998

Initialed by: L.Talarico/November 3, 1998

Initialed by: H.Gallo-Torres/October 28, 1998

Initialed by: J.Choudary/October 31, 1998

Initialed by: J.Hunt/October 30, 1998

Initialed by: E.Duffy/November 3, 1998

Initialed by R.Frankewich/November 2, 1998

Initialed by: A.Sankoh/November 3, 1998

final: A.Kacuba/November 5, 1998

filename: n:\meeting\1998\19797A10.doc

MEETING MINUTES

Food and Drug Administration
Rockville MD 20857

IND 28,741

AUG 25 1993

Braintree Laboratories, Inc.
Attention: Ms. Vivian Caballero
60 Columbian Street, P.O. Box 361
Braintree, MA 02184

Dear Ms. Caballero:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for NuLytely (PEG 3350, Sodium Chloride, Sodium Bicarbonate and Potassium Chloride for Oral Solution).

We also refer to the meeting held on June 9, 1993, between representatives of your firm and this Agency. The following represents our summary of the meeting.

MEMORANDUM OF MEETING
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

IND 28,741, NuLytely
June 9, 1993
Protocol Discussion

BETWEEN

BRAINTREE LABS:

Dr. Geoff Clark-Medical Director

Dr. Mark Cleveland-New Product Development
Ms. Vivian Caballero-Regulatory Affairs

AND

FOOD AND DRUG ADMINISTRATION, HFD-180:

Dr. Stephen B. Fredd-Division Director
Ms. Kati Johnson-Consumer Safety Officer

FOOD AND DRUG ADMINISTRATION, HFD-715:

Dr. Mohammad Huque-Statistical Group Leader
Dr. Ferrin Harrison-Statistician

BACKGROUND

NuLytely was approved April 22, 1991 as a 4.3 liter (L) HDPE bottle containing powder for constitution to 4 liters. It is one of several orally administered products available (GoLytely,

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CoLyte, OCL) for bowel cleansing prior to colonoscopy and/or barium enema x-ray examination. The labeling insert states that at least 3 L is generally required to produce a watery stool.

The firm requested a meeting to discuss protocol F38-10 entitled, "Reduced NuLytely Dose Regimen", in which they plan to study a 2 L dose NuLytely regimen (using a cherry flavored formulation) which includes oral pre-preparation with 20 mg bisacodyl.

MEETING

Regulations, 21 CFR 300.50, require that the contribution of each component of a combination treatment be determined. Dr. Fredd suggested that a factorial study design be employed to demonstrate the contribution of each ingredient of the proposed combination, using either placebo (PBO) or an historical control, although the latter provides less compelling evidence of efficacy. Dr. Fredd suggested the protocol include the following treatment arms: NuLytely alone, dosed until rectal effluent is clear, bisacodyl alone, and the combination of the two. Dr. Fredd recommended that the Cherry Flavor be removed from the formulation being investigated since that is not the currently approved formulation.

It was Dr. Fredd's position that sufficient information is available to document the ineffectiveness of bisacodyl as a single agent for bowel cleansing, thus obviating the need for a bisacodyl alone treatment arm. Dr. Fredd indicated that since bisacodyl is an ingredient that was reviewed under the OTC Monograph for Laxative Drug Products [refer to the Tentative Final Monograph (TFM)], its efficacy, from a regulatory perspective, has been determined. In response to a question from the firm, Dr. Fredd stated that if bisacodyl is not listed as "effective" under the monograph, this information combined with literature MAY suffice to justify deleting the bisacodyl alone arm.

Instead of a fixed 2 L dose in the combination treatment arm, as proposed, Dr. Fredd suggested that patients be given sufficient powder to constitute to 4 L of solution and then determine how much is required to achieve a clear rectal effluent.

The firm said that they plan to evaluate patient preference of the combination treatment as an endpoint. The firm also offered that the Australian study, summarized in the pre-meeting document, demonstrated equivalence of the combination and the 4 L preparation in achieving "excellent" preparation and, in addition, a decrease in the amount of nausea. Dr. Fredd

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questioned whether this conclusion would hold up under statistical analysis. He suggested that the primary endpoint might be "excellent" cleansing if the firm is wedded to a fixed dose comparison study with a hypothesis that the combination is equivalent to 4 liters of NuLytely in terms of colonoscopy results. Secondary endpoints might include the incidence of adverse events, the achievement of "good" cleansing, and decreased fluid requirement for NuLytely. He cautioned that the study must be sized to demonstrate equivalence between the combination and the approved 4 L preparation and that the combination treatment is statistically superior to bisacodyl alone, if this arm is required.

Dr. Fredd estimated that, based on standards applied to generic drug applications (ANDAs), approximately 100 patients would be required in each treatment arm to demonstrate equivalence ($\pm 20\%$) between the two treatments. He suggested the firm evaluate various sample sizes required to achieve a stated statistical power, to determine what is clinically feasible. He also suggested that this information (preferably in tabular form) be submitted for comment.

In response to the firm's question of whether approval of the combination treatment will require two studies, Dr. Fredd said that what would be needed for approval cannot be determined until studies are reviewed. However, if one study was conducted and the results were very strong, e.g., strongly significant results for both primary and secondary endpoints, then one study could possibly be sufficient for approval, but not with a single center.

Dr. Fredd noted that while the nature of the treatment arms make it impossible to blind the patients as to which treatment they have been randomized to receive, it is essential that the person responsible for evaluating the colonoscopy be blinded. The firm assured him that the physicians performing as well as evaluating the colonoscopies will be blinded.

Dr. Fredd inquired about the availability of information regarding a possible association between bisacodyl and the fluid transport system which could affect the safety of the combination product. The firm responded that animal data is available to demonstrate that it has no effect on PEG 4000 absorption, which would in turn effect fluid transport. Dr. Fredd suggested this be evaluated in the patient population through the monitoring of electrolytes and osmolarity.

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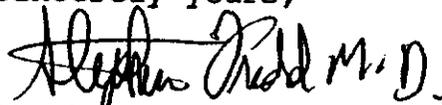
Dr. Huque had the following comments on the statistical portion of the protocol:

1. The randomization scheme should be clarified. If the study is multicenter, the protocol should indicate the block size. If there are 3 treatment groups, he advised against balancing the randomization with 3 patients. Dr. Fredd stressed that the treatment assignments follow the randomization plan.
2. The protocol, as submitted, does not state the primary statistical hypothesis. Demonstration of equivalence between treatment involves rejecting the hypothesis of some difference. The study should be powered accordingly. He suggested a 90% confidence interval.
3. Analyses should include the Wilcoxon test. He advised against using either the Odds Ratio or Relative Risk statistical test.

If you have any questions concerning this IND, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,



Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research