CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203595Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # NDA 203595 SUPPL # HFD #

Trade Name Suclear

Generic Name: sodium sulfate, potassium sulfate and magnesium sulfate oral solution; and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution

Applicant Name Braintree Laboratories, Inc

Approval Date, If Known 1-18-13

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES X NO ☐

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

NA

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:

NA

d) Did the applicant request exclusivity?

YES X NO ☐

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

Sponsor did not specify how many years

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

YES ☐ NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NA

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO X

IF THE ANSWER TO QUESTION 2 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#

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#	21-551 (Halflytely),19-797 (Nulytely),19-011 (Golytely), 18-983 (Colyte)	PEG-3350, sodium chloride, sodium bicarbonate, potassium chloride
NDA#	22-372 (Suprep)	Sodium sulfate, potassium sulfate, magnesium sulfate
NDA#	21-881 (MoviPrep)	PEG-3350, sodium sulfate, sodium chloride, potassium chloride

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 ☐

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:

BLI850-301, BLI850-302

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

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 (BLI850-301) YES ☐ NO X

Investigation #2 (BLI850-302) YES ☐ NO X

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

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 (BLI850-301) YES ☐ NO X

Investigation #2 (BLI850-302) YES ☐ NO X

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

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

BLI850-301, BLI850-302

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 (BLI850-301)

IND # 102894 YES X NO ☐
Explain:

Investigation #2 (BLI850-302)

IND # 102894 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 ☐ NO ☐
Explain: Explain:

Investigation #2

YES ☐ NO ☐
Explain: 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:

==========

Name of person completing form: Matthew Scherer
Title: Regulatory Project Manager
Date: 1-18-13

Name of Office/Division Director signing form: Donna Griebel
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

MATTHEW C SCHERER
01/18/2013

DONNA J GRIEBEL
01/18/2013

LABORATORIES • INC
Braintree

NDA 203595
[redacted] (b) (4), sodium sulfate, potassium sulfate and magnesium sulfate and PEG-3350 and [redacted] (b) (4) for oral solution)

Debarment Certification:

Braintree Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Mark vB. Cleveland, Ph.D.

10/17/11
Date

Vice President, New Product Development
Braintree Laboratories, Inc.

Scherer, Matthew

From: Scherer, Matthew
Sent: Friday, January 04, 2013 12:10 PM
To: 'Caballero, Vivian'
Subject: NDA 203595 (Suclear) - requested revisions to IFU

Attachments: Comments on IFU.doc

Hello Vivian,
Attached, please find a draft of the patient instruction for use with requested revisions. Please revise accordingly and submit to the NDA.

Best regards,
Matt

Comments on IFU.doc (174 KB)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MATTHEW C SCHERER
01/04/2013

Scherer, Matthew

From: Scherer, Matthew
Sent: Friday, January 04, 2013 12:58 PM
To: 'Caballero, Vivian'
Subject: NDA 203595 (Suclear) - revisions to medication guide

Attachments: comments on MG.doc

Hello Vivian,
Attached, please find our requested revisions to the Suclear Medication Guide. Please revise accordingly and submit to the NDA.

Kind regards,
Matt

comments on MG.doc (93 KB)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MATTHEW C SCHERER
01/04/2013

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TELECON MEETING MINUTES

Meeting Date and Time:	December 10, 2012 2:00 PM
Application Number:	203595
Product Name:	Suclear (BLI850)
Indication:	indicated for cleansing of the colon in preparation for colonoscopy in adults
Applicant Name:	Braintree Laboratories, Inc.
Meeting Chair:	Robert Fiorentino, M.D., M.P.H.
Meeting Recorder:	Maureen Dewey, M.P.H.

FDA ATTENDEES

Joyce Korvick, M.D., M.P.H., Deputy Director for Safety
Robert Fiorentino, M.D., M.P.H., Medical Team Leader
Jessica Lee, M.D., Medical Officer
Sue Chih Lee, Ph.D., Supervisory Clinical Pharmacologist
Teresa McMillan, DMEPA Reviewer
Carlos Mena-Grillasca, DMEPA Team Leader
Gene Holbert, Ph.D., CMC Reviewer
LaRee Tracy, Pharm.D, Safety Statistics
Brad McEvoy, Pharm.D., Safety Statistics
Karen Dowdy, Patient Labeling
Kendra Jones, OPDP
Maureen Dewey, Regulatory Project Manager

APPLICANT ATTENDEES

Braintree Laboratories, Inc.
Mark Cleveland, Sr. VP R&D
John McGowan, Director, Clinical Research
James Banschbach, VP Quality/Compliance
Vivian Caballero, VP Regulatory Affairs
John O'Neil, Manager, Material Control

1.0 BACKGROUND

The Division received the applicant's NDA 203595 on December 19, 2011. BLI850 consists of (1) sodium sulfate, potassium sulfate and magnesium sulfate oral solution; and (2) PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution. The Applicant's proposed indication is "for cleansing of the colon in preparation for colonoscopy in adults".

2.0 DISCUSSION

I. The "fill line" on cup and patient instructions for use

a. The Division reiterated concerns regarding the lack of prominence of the fill line on the cup as well as on the patient's instructions for use. The sponsor stated that the mold for the cup is set and cannot be altered (b) (4) The Division clearly stated that in the long term the cup design is not satisfactory and it is likely that changing the cup design will be a post marketing commitment.

b. DMEPA reiterated concerns regarding the current mixing cup that is illustrated in the instructions for use and on the carton labeling since it is not an actual representation of the proposed mixing cup and does not clearly identify the fill line. The following improvements were suggested to the sponsor: using an actual picture of the mixing cup that "zooms" in on the fill line and the use of an arrow to identify the fill line on all illustrations. The sponsor agreed to check with their vendors on drafting new illustrations. The sponsor will provide the Regulatory Project Manager with an updated timeline for the submission of the revised illustrations.

II. The Division inquired whether during the phase 3 clinical trials there were specific instructions for patients to finish dose 1. The sponsor stated they did not specify a set end time. The patients started the first dose at approximately 6:00 pm. Then, they consumed 16-oz of water over the next 2 hours. There was no time specified for consuming the last 16-oz of water before going to bed (in split-dose regimen). The sponsor agreed to look back at the case report forms to determine whether timing (start to finish) of first dose was captured.

III. Discussion of revised PMRs (FDAAA and PREA):

The sponsor proposed additional 6 months for the final protocol submission from: December 1, 2013 to June 2014. The rationale provided was that the sponsor still needs to develop an assay (b) (4) which may take up to one year. Further, the sponsor stated that it would be beneficial to have completed the Suprep study in order to design a better study for Suclear. The Division requested the sponsor to resubmit the revised milestone dates for the PMRs along with a justification for the Division to review.

IV. Update on development of an assay to detect the presence of impurities (b) (4)

The sponsor stated that they are on target with the goal date of January 1, 2013.

2.0 ACTION ITEMS

a) Sponsor to revise the illustrations on the instructions for use and carton labeling to be representative of the actual cup
   - Incorporate a zoom in to show the "fill line" area.

b) Sponsor to continue evaluation of alternate cup design that would provide for colored fill line.

c) Sponsor to review CRFs to determine whether timing (start to finish) of first dose was captured.

d) Sponsor to propose language for timing on administration of first dose.

e) Sponsor to submit proposed timing on PMRs with discussed rationale on dates.

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/s/

MAUREEN D DEWEY
12/12/2012
do not mail, internal meeting minutes only

Scherer, Matthew

From: Scherer, Matthew
Sent: Thursday, December 06, 2012 12:39 PM
To: 'Caballero, Vivian'
Subject: NDA 203595 (Suclear) - revised PMRs

Attachments: FDAAA and PREA 12-6-12.pdf

Hi Vivian,
Attached, please find a revised list of required postmarketing studies (both PREA and FDAAA). Please submit a letter of concurrence to the NDA.

Best regards,
Matt
-
Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993

FDAAA and PREA 12-6-12.pdf (17...

FDAAA Required Studies

PMR #1 An adequate randomized, active control, single-blind trial to evaluate renal dysfunction and laboratory abnormalities in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking SUCLEAR prior to colonoscopy. Serial laboratory and clinical assessments should be done at regular pre-specified intervals for at least 30 days post-treatment.

- Final Protocol submission: December 1, 2013
- Study/Trial completion: December 1, 2015
- Final report submission: June 1, 2016

PMR #2 Assess the systemic exposure and pharmacokinetics of PEG3350, (b) (4) following oral administration of SUCLEAR to adult subjects. These assessments may be conducted as a sub-study of PMR #1 (above).

- Final Protocol submission: December 1, 2013
- Study/Trial completion: September 1, 2014
- Final report submission: December 1, 2014

PREA Required Studies

Study 1: An open-label pilot study assessing the efficacy and tolerability of BLI850 in pediatric patients ages 12-16 years, inclusive.

- Final Protocol submission: December 1, 2013
- Study/Trial completion: September 1, 2014
- Final report submission: March 1, 2015

Study 2: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in adolescents (12-16 years of age, inclusive).

- Final Protocol submission: March 1, 2015
- Study/Trial completion: March 1, 2016
- Final report submission: September 1, 2016

Study 3: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in children (3-11 years of age, inclusive).

- Final Protocol submission: September 1, 2016
- Study/Trial completion: September 1, 2017
- Final report submission: March 1, 2017

Study 4: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in children (1-2 years of age, inclusive).

- Final Protocol submission: March 1, 2018
- Study/Trial completion: March 1, 2019
- Final report submission: September 1, 2019

Study 5: Assess the systemic exposure and pharmacokinetics of PEG 3350, (b) (4) following oral administration of SUCLEAR in an adequate number of pediatric patients, encompassing all relevant age groups. Assessments listed under study 5 may be conducted as part of the PREA required studies listed above.

- Final Protocol submission: March 1, 2018
- Study/Trial completion: March 1, 2019
- Final report submission: September 1, 2019

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/s/

MATTHEW C SCHERER
12/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595

REVIEW EXTENSION – MAJOR AMENDMENT

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Vice President, Regulatory Affairs
60 Columbian Street West
PO Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Suclear (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350 and (b) (4) Oral Solution.

On August 13, 2012, we received your August 10, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 19, 2013.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301)796-2307.

Sincerely,

{See appended electronic signature page}

Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
10/10/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Wednesday, October 03, 2012 8:54 PM
To: 'Caballero, Vivian'
Cc: Stephenson, Franklin
Subject: NDA 203595 (Suclear) - comments regarding container and carton labeling

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 Suclear.

We are reviewing your proposed carton, container and related labeling and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please contact Franklin Stephenson and myself.

Best regards,

Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993

A. General

Present the established name wherever presented on the labels and labeling as the following:

(Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate) Oral Solution and (PEG-3350 and Sodium Bicarbonate, Sodium Chloride, Potassium Chloride) for Oral Solution

B. Mixing Cup

1. The following statement is not legible because it appears in a clear font against a clear background on the cup: "16-oz. Fill Line". Revise this statement so that there is sufficient color contrast against the clear background or redesign so that the lettering and the fill line are prominent and can be read.
2. The fill line instruction appears between two horizontal lines. Although, there are arrows pointing to the fill line, this line is thin and opaque, thus making the line virtually illegible on the cup. Also, the top line is thick and the user may confuse the two lines and fill the product to the incorrect line. Revise the cup and consider using a transparent non-indented mixing cup so that a 16 oz. fill line can be easily seen and read by the end user.
3. Delete the following statement: [redacted] (b) (4) because the statement is misleading. The patient must drink an electrolyte solution and water.
4. Add the proprietary name for this product to the mixing cup so that it is identified for use with this product.

C. Reconstitution Container

1. The fill line is not recognizable because it is not prominent. Increase the prominence of the fill line so that it is more recognizable.
2. The "Fill Line" statement is not legible because it appears in a clear font against a clear background on the bottle and lacks prominence. Revise this statement so that there is sufficient color contrast against the clear background.

D. **All Labels and Labeling**

The 16 oz. mixing device is identified as a cup and/or a container throughout the labels and labeling. For consistency and to avoid confusion, select only one term to represent the 16 oz. device when referenced throughout the labels and labeling.

E. **Prescribing Information**

1. Dosage and Administration (Highlights and Full Prescribing Information):
   a) To maintain consistency of the presentation of information throughout the Prescribing Information add the following statements to appear before the "Add water to the 2 liter fill line on the jug" statement in the Split Dose (2 -day) and the (b) (4) (1-Day) Regimens:

      Optional-Add 1 flavor pack of choice to the 2 liter bottle. Solution can be used with or without flavor packs.

   b) The word ounce and the abbreviation for ounce (oz) both appear in the "Drink all the solution at a rate of 16 oz ounces every 20 minutes" sentence in the Split Dose (2-Day) Regimen section. To avoid confusion, delete the abbreviation for ounce in this sentence.
2. How Supplied/Storage and Handling:

   List the optional Flavor Pack Flavors under the "Each Suclear kit contains" subheading because they are supplied in the kit.
3. Patient Instructions for Use Booklet:
   a) The information on Pages 2 and 3 of the Patient Instructions for Use Booklet does not read in sequential order in the usual reading format from top to bottom from one page to the next. As currently presented, the information can be read out of sequence and lead to confusion. Present the Patient Instructions for Use on pages 2 and 3 in sequential order from top to bottom on one page and then continue in sequential order from top to bottom on the next page.
   b) Remove the (b) (4) from the Patient Instructions For Use handbook because this information is written for healthcare practitioners.
   c) Remove the statement (b) (4) from the cover of the Patient Instructions for Use Booklet because this information is written for healthcare practitioners.
   d) Pages 2 and 3 use a lime green color against a white background to highlight certain terms under the following headings: "What to eat and drink on the day before your procedure" and "Any of the following clear liquids are okay to drink". As presented these terms are not distinctly visible. Provide a better contrast in color to highlight these terms.

F. **Carton Labeling**

1. Include the product strength on the principal display panel of the carton labeling. For example under the "Dose 1" heading on the principal display panel state the following:

   One 6 ounce (177 mL) bottle of Sodium Sulfate 17.5 g, Potassium Sulfate 3.13 g, and Magnesium Sulfate 1.6 g Oral Solution

   For example under the "Dose 2" heading on the principal display panel present as the following:

One 2-liter bottle of PEG-3350 210 g, Sodium Bicarbonate 2.86 g, Sodium Chloride 5.6 g, and Potassium Chloride 0.74 g for Oral Solution

2. Remove the [redacted] which appear in the proprietary name.
3. Replace the name [redacted] that appears on the top opening of the carton with the approved proposed proprietary name.
4. Remove the number "1" wherever it appears on the principal display panel under the heading "This Carton Contains" and replace it with the word "one". The placement of two numbers next to each other, even with the use of highlighting one of the numbers, as presented in this case, may be confusing because a patient or healthcare practitioner may misinterpret this presentation as '16 ounce', '116 ounce', or '12 liters'.
5. Revise the statement [redacted] on the principal display panel to state the following:

   Full Prescribing Information and One Patient Instruction Booklet with the Medication Guide
6. Increase the prominence of the following statement which appears on the Principal display panel: "Dispense the enclosed Medication Guide to each patient".
7. Increase the prominence of the following statement which appears on the Principal display panel: "NOTE: both doses are required for a complete prep" to be commensurate to the statement "Dilute As Directed Prior to Use" and relocate to appear above the storage statement.

G. **Container Labels**

1. Increase the prominence of the "For use with Suclear kit only" statement on the "Dose 1" and "Dose 2" container labels. Additionally relocate the statement to appear above the "Dose 1" and "Dose 2" statements.
2. Revise the [redacted] statement that appears on the "Dose 1' and 'Dose 2" container labels to state the following:

   "See complete instructions in the enclosed booklet or on the box before using."
3. Revise the directions on the "Dose 2" container label to state the following:

   "Add 1 flavor pack. Add drinking water to the top of the fill line on the bottle. Shake. Drink one (16 oz.) glass of solution every 20 minutes. Drink all the solution."
4. Delete the [redacted] statement that appears after the strength on the "Dose 2" container label because this information is redundant and is presented elsewhere on the label.

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/s/

MATTHEW C SCHERER
10/03/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Wednesday, October 03, 2012 9:43 PM
To: 'Caballero, Vivian'
Subject: NDA 203595 (Suclear) - required postmarketing studies

Dear Ms. Caballero,

Below, please find a summary description of the required postmarketing studies we are seeking for Suclear. Note that the included milestone dates are based on an approval date in October 2012.

Please submit a response indicating your concurrence as soon as possible.

Best regards,

Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993

PMR #1

PMR/PMC Description:	An adequate randomized, active control, single-blind trial to evaluate renal dysfunction and laboratory abnormalities in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking SUCLEAR prior to colonoscopy. Serial laboratory and clinical assessments should be done at regular pre-specified intervals for at least 30 days post-treatment.	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/01/2013
	Study/Trial Completion:	03/01/2015
	Final Report Submission:	09/01/2015
	Other:	MM/DD/YYYY

SUCLEAR PMR #2

PMR/PMC Description:	Assess the systemic exposure and pharmacokinetics of PEG3350, [redacted] (b) (4) following oral administration of SUCLEAR to adult subjects. These assessments may be conducted as a sub-study of PMR #1.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/01/2013
	Study/Trial Completion:	03/01/2015
	Final Report Submission:	09/01/2015
	Other:	MM/DD/YYYY

PREA

Study 1: An open-label pilot study assessing the efficacy and tolerability of BLI850 in pediatric patients ages 12-16 years, inclusive. This study will include PK assessments.

- Protocol submission: October 31, 2013
- Study completion: July 31, 2014
- Study report submission: October 31, 2014

Study 2: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in adolescents (12-16 years of age, inclusive). This study will include PK assessments.

- Protocol submission: January 31, 2015
- Study completion: January 31, 2016
- Study report submission: April 30, 2016

Study 3: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in children (3-11 years of age, inclusive). This study will include PK assessments.

- Protocol submission: July 31, 2016
- Study completion: July 31, 2017
- Study report submission: October 31, 2017

Study 4: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of BLI850 (up to 3 doses) versus community standard of care in children (1-2 years of age, inclusive). This study will include PK assessments.

- Protocol submission: January 31, 2018
- Study completion: January 31, 2019
- Study report submission: April 30, 2019

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/s/

MATTHEW C SCHERER
10/03/2012

Scherer, Matthew

From: Scherer, Matthew
Sent: Tuesday, September 18, 2012 9:50 PM
To: 'Caballero, Vivian'
Subject: NDA 203595 (BLI850) - preliminary PI comments

Attachments: (b) (4) PI draft sent 9-18-12.doc

Hello Vivian,
Attached, please find the Division's preliminary response to your proposed labeling. Please note that we expect to have additional comments as we continue to progress on our reviews and have additional discussions. Furthermore, please note the following:

1. The Highlights and Table of Contents should be revised to be consistent with the Full Package Insert
2. The Container/Carton, Medication Guide and booklet should be consistent, as appropriate, with the package insert
3. We will send separate comments on the container/carton labeling and patient labeling (including Container/Carton, Medication Guide and booklet)
4. Required postmarketing studies (PMRs) and/or postmarketing commitments (PMCs) will be sent in a separate communication

Please submit revised labeling and send a copy to me in word format by Wednesday, September 26, 2012.

Kind regards,
Matt

(b) (4) PI draft sent 9-18-12.d...

-
Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MATTHEW C SCHERER
09/18/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 203595

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Braintree Laboratories, Inc
60 Columbian Street West
P.O. Box 850929
Braintree, MA 02185

ATTENTION: Vivian A. Caballero
Vice President, Regulatory Affairs

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate Oral Solution and PEG-3350, Sodium Bicarbonate, Sodium Chloride, Potassium Chloride for Oral Solution, 17.5 g/3.13 g/1.6 g and 210 g/2.86 g/5.6 g/ (b) (4)

We also refer to your June 21, 2012, correspondence, received June 22, 2012, requesting review of your proposed proprietary name, Suclear. We have completed our review of the proposed proprietary name, Suclear and have concluded that it is acceptable.

The proposed proprietary name, Suclear, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your June 21, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Scherer at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/17/2012

Tran-Zwanetz, Catherine

From: Tran-Zwanetz, Catherine
Sent: Friday, September 14, 2012 3:11 PM
To: 'Caballero, Vivian'
Subject: NDA 203595 new IR

HI Vivian,

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide a revised specification table for your drug substance, incorporating the (b) (4) limit for (b) (4) plus (b) (4), and provide the method that will be used to test for these impurities. USP <467> Residual Solvents is not sufficient for this purpose.

2. Please amend your application to indicate that Braintree will test every batch of polyethylene glycol drug substance for (b) (4) plus (b) (4) content. Relying on the supplier's certificate of analysis will not be sufficient.

Please provide your response as soon as possible.

If possible please send me an electronic copy as well as a formal amendment to the NDA. Could you also please send me an electronic version of your response from September 7, 2012.

Please let me know if you have any questions.
Cathy Tran-Zwanetz
Regulatory Project Manager
(301) 796-3877

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/s/

CATHERINE A TRAN-ZWANETZ
09/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595 **INFORMATION REQUEST**

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Vice President, Regulatory Affairs
60 Columbian Street West
PO Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for BLI-850 (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350 and (b) (4)) Oral Solution.

We have reviewed your response to the information request dated August 3, 2012, and have the following additional questions. Please respond promptly so we can continue to review your NDA.

1. In order to better understand the appropriateness of comparing percent stool solids ("scatocrit") resulting from different cleansing regimens, provide information on how subjects' diet and liquid intake were standardized before, during and after administration of the bowel preparation. If available, submit the protocol used for these studies.

2. Describe in detail how scatocrit was measured, including the amount of diarrheal sample used and the formula that was used for calculation. If a different method of scatocrit calculation was used for any of the following bowel preparations listed in Table 2 of your August 3, 2012 submission, specify the difference: 2L NuLYTELY, Sulfate Solution 5 (22g SO_4), 4L NuLYTELY, HalfLytely (with 20 mg bisacodyl), SUPREP, and Solution 4 (Sulfate + 2L NuLYTELY).

3. Provide a table comparing the amount of each salt (i.e., Na_2SO_4, KSO_4, $MgSO_4$) in Sulfate Solution 5 (used in Baylor 005-082) and BLI800 (or SUPREP). It is important to demonstrate that Sulfate Solution 5 is equivalent to half of BLI800 (or SUPREP).

4. To better facilitate comparison, include results from the following bowel preparations in all figures included in August 3, 2012 submission: 2L NuLYTELY, Sulfate Solution 5 (22g SO_4), 4L NuLYTELY, HalfLytely (with 20 mg bisacodyl), SUPREP, and BLI850.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Brian Strongin, RPh, MBA
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
08/24/2012

Tran-Zwanetz, Catherine

From: Tran-Zwanetz, Catherine
Sent: Thursday, August 09, 2012 4:37 PM
To: 'Caballero, Vivian'
Cc: Scherer, Matthew
Subject: NDA 203-595 IR

HI Vivian,

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Regarding the Drug Product:

- Provide batch analysis data for unflavored SUCLEAR Part 2. The information submitted in section 3.2.P.5.4 Batch Analysis is for the lemon-lime flavored product.
- The supplier of the flavoring in the flavor packets has been identified as (b) (4) Identify the manufacturer of the flavor packets and submit a copy of the flavor packet labeling.
- Clarify the purpose/use of (b) (4) purchased from (b) (4) and submit a COA for (b) (4) (b) (4) The page inserted at tab #5 (b) (4) is blank.
- Specify the expiration dating period of the flavor packets.
- The executed batch record submitted pertains to the Lemon-Lime PEG-ELS flavored finished product. The current application is for a formulation with favoring to be added by the patient as desired. Submit a batch record for a batch of unflavored drug product with the attached flavor packs.

Please provide your response along with your responses to our other Information Request regarding (b) (4) and (b) (4) (b) (4) levels by September 7, 2012.

Please let me know if you have any questions.
Cathy Tran-Zwanetz
Regulatory Project Manager
(301) 796-3877

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/s/

CATHERINE A TRAN-ZWANETZ
09/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595 **INFORMATION REQUEST**

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Vice President, Regulatory Affairs
60 Columbian Street West
PO Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for BLI-850 (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350 and (b) (4)) Oral Solution.

In order to evaluate whether the Combination Rule (21 CFR 300.50) is adequately addressed within the NDA, provide the following:

1) Demonstration that the combination product (i.e., BLI850) would be superior to each component alone (i.e., 6 ounces of Suprep or 2 liters of Nulytely)

2) Provide clinically relevant data and/or literature to demonstrate that each component of BLI850 by itself will result in inadequate bowel cleansing prep

For each of the above, provide the data that support the use of "scatocrit" as a clinically relevant measure to predict bowel cleaning efficacy. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
08/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595

INFORMATION REQUEST

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Vice President, Regulatory Affairs
60 Columbian Street West
PO Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for BLI-850 (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350 and (b) (4)) Oral Solution.

We are reviewing the clinical and chemistry, manufacturing and controls sections of your submission and have the following requests for information. We request a prompt written response in order to continue our evaluation of your NDA.

1. Submit the datasets listed in the table, below, only including patients who have received treatment with BLI-850, HalfLytely, or MoviPrep (i.e., ITT population) for (a) Study 301, (b) Study 302, and (c) Studies 301 and 302 combined. Please do not submit datasets that include all randomized patients, since some of these patients did not receive treatment. The maximum number of patients included in these datasets should be 366 for Study 301 (176 patients in the BLI-850 treatment arm and 190 patients in the HalfLytely treatment arm), 371 for Study 302 (186 patients in the BLI-850 treatment arm and 185 patients in the MoviPrep treatment arm), and 737 for Studies 301 and 302 combined (362 patients in the BLI-850 treatment arm, and 375 patients in HalfLytely and MoviPrep treatment arms combined).

Requested Datasets:

Study 301	Study 302	Studies 301 + 302 combined	Description of Dataset
AE	AE2	AE2	Adverse event
AESY	AESY2	AESY2	Adverse event plus symptoms
DM	DM	DM	Demographics
LL	LL	LL	Laboratory results
SY	SY	SY	Symptom scale
VS	VS	VS	Vital signs

Provide these datasets (in .xpt format) by July 24, 2012.

2. As discussed during the July 16, 2012, teleconference, revise your specification for PEG 3350 to reflect the Agency's proposed acceptance criterion of [redacted] for combined [redacted] and [redacted] to comply with the ICH PDE limit of [redacted]. Describe in detail the analytical procedure to be used, if different from that in Pharmacopeial Forum 31 (3), pp. 897-904.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
07/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595

INFORMATION REQUEST

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Vice President, Regulatory Affairs
60 Columbian Street West
PO Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350 and (b) (4) Oral Solution.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In order to better understand the reasons subjects were included or excluded from the laboratory shift analysis in studies 301 and 302, we are requesting a modified laboratory dataset for each study. The modified dataset should present the details of the observed laboratory values, and if the values are not available, the reason(s). For example, we would like to understand the reasons for missing albumin values of the 16 subjects in study 301 who received BLI850 and were excluded from the shift table for albumin (refer to Table 14.3.6.1 and Table 301-21 in the CSR). For each study, please submit a dataset that has one row per visit per laboratory test per subject which includes the following variables:

Variable name	Label	Type	Notes
usubjid	Unique subject identifier	Char	
studyid	Study identifier	Char	
lbtest	Name of laboratory test	Char	
itt	Intent-to-treat indicator	Numeric	1 if patient is in the ITT group, 0 else
rtrt	Treatment randomized	Char	
atrt	Actual treatment received	Char	
visit	Visit number	Char	
lbdate	Date of sample	Numeric	
lborres	Laboratory result	Numeric	
lborresu	Unit of laboratory result	Char	e.g., g/L
lbornrlo	Lower limit of normal	Char	Lower limit of normal reference lab value in the same unit
lbornrhi	Upper limit of normal	Char	Upper limit of normal reference lab value in the same unit

lbstat	Lab completion status	Char	Indicate whether lab exam not performed or result is unavailable. Should be null if result exists in lborres
lbreasnd	Reason test not done or result unavailable	Char	Describes why test or measurement was not performed or result is unavailable (e.g., hemolyzed serum). Should be null if lbstat is null
lbredraw	Indicator for redraw	Numeric	1 if redraw
lbrdrwv	Visit when sample redrawn	Numeric	Visit when the sample was redrawn
lbrdrwr	Reason for redraw	Char	Explanation for redrawing sample
rnovst2	Reason visit 2 not performed	Char	Explanation why patient did not have laboratory measurements for visit 2 (e.g., withdrew consent). Should be null if subject has visit 2 measurements
sex	Sex of patient	Char	
age	Age in years of patient	Numeric	
highrisk	High risk patient indicator	Numeric	1 if patient has medical history of cardiac, renal or vascular problems (hypertension), or diabetes, 0 else

Refer to the next page for an example of the requested dataset.

In addition to the information requested above, please provide any additional information that might aid in the evaluation of laboratory data for those subjects with and without measurements. You may include additional variables in the requested datasets, patient summaries or tables. If variables are added to the requested datasets, please include detailed descriptions of the variables.

Please provide the requested datasets (in .xpt format) by July 20, 2012.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., MBA
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Narrative

Patient 10001 (rows 1-4): Measurements at visits 1 and 2 were collected as per protocol.
Patient 10002 (rows 5-10): Had redraw for visit 2 since the visit 2 samples hemolyzed.
Patient 10003 (rows 11-12): Only had baseline values as she was unable to make the visit 2 appointment.

	usubjid	studyid	Lbtest	itt	rtrt	visit	Lbdate	lborres	lborresu	lbornrlo	lbornrhi
Row 1	10001	301	ALBUMIN	1	BLI850	1	2010-06-12	33	mg/L	30	55
Row 2	10001	301	ALBUMIN	1	BLI850	2	2010-06-20	34	mg/L	30	55
Row 3	10001	301	CHLORIDE	1	BLI850	1	2010-06-12	45	mg/L	40	65
Row 4	10001	301	CHLORIDE	1	BLI850	2	2010-06-20	42	mg/L	40	65
Row 5	10002	301	ALBUMIN	1	BLI850	1	2010-07-12	38	mg/L	30	55
Row 6	10002	301	ALBUMIN	1	BLI850	2	2010-07-20		mg/L	30	55
Row 7	10002	301	ALBUMIN	1	BLI850	2 Redraw	2010-08-01	55	mg/L	30	55
Row 8	10002	301	CHLORIDE	1	BLI850	1	2010-07-12	57	mg/L	40	65
Row 9	10002	301	CHLORIDE	1	BLI850	2	2010-07-20		mg/L	40	65
Row 10	10002	301	CHLORIDE	1	BLI850	2 Redraw	2010-08-01	65	mg/L	40	65
Row 11	10003	301	ALBUMIN	1	BLI850	1	2010-06-29	45	mg/L	30	55
Row 12	10003	301	CHLORIDE	1	BLI850	1	2010-06-29	60	mg/L	40	65

	lbstat	lbreasnd	lbredraw	lbrdrwv	lbrdrwr	rnovst2	sex	age	highrisk
Row 1 (cont)							M	65	0
Row 2 (cont)							M	65	0
Row 3 (cont)							M	65	0
Row 4 (cont)							M	65	0
Row 5 (cont)							F	38	1
Row 6 (cont)	Incomplete	Hemolyzed serum					F	38	1
Row 7 (cont)			1	2	Visit 2 serum hemolyzed		F	38	1
Row 8 (cont)							F	38	1
Row 9 (cont)	Incomplete	Hemolyzed serum					F	38	1
Row 10 (cont)			1	2	Visit 2 serum hemolyzed		F	38	1
Row 11 (cont)						Unable to make appt	F	63	1
Row 12 (cont)						unable to make appt	F	63	1

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/s/

BRIAN K STRONGIN
07/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595

PROPRIETARY NAME REQUEST WITHDRAWN

Braintree Laboratories, Inc
60 Columbian Street West
P.O. Box 850929
Braintree, MA 02185

Attention: Vivian A. Caballero
Vice President, Regulatory Affairs

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate Oral Solution and PEG-3350, Sodium Bicarbonate, Sodium Chloride, Potassium Chloride for Oral Solution.

We acknowledge receipt of your correspondence, dated June 21, 2012 and received June 22, 2012, notifying us that you are withdrawing your May 31, 2012 request for a review of the proposed proprietary name (b) (4) This proposed proprietary name request is considered withdrawn as of June 22, 2012.

We also acknowledge that your correspondence dated June 21, 2012, requests review of your proposed name, Suclear.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Scherer at (301) 796-2307.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/05/2012

MEMORANDUM DEPARTMENTOF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 20, 2012
TO: Administrative File, NDA 203595

FROM: Nitin M. Patel.
Project Manager
Office of Surveillance and Epidemiology

APPLICATION: NDA 203595: (b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate + PEG-3350, sodium bicarbonate, sodium chloride, potassium chloride)

APPLICANT: Braintree Laboratories, Inc.

SUBJECT: DMEPA requested this teleconference to inform the Applicant of our concerns with the proposed proprietary name (b) (4) and in particular the fact that the proprietary name contains the United States Adopted Name (USAN) stem (b) (4)

Participants: *FDA*: Lubna Merchant, PharmD, M.S. Team Leader, DMEPA
Anne Tobenkin, PharmD, Safety Evaluator, DMEPA
Nitin M. Patel, Project Manager, OSE

(b) (4)

Issues:

Although DMEPA is still in the preliminary stage of the review of the proposed name (b) (4) DMEPA wanted to notify the Sponsor that we have concerns with the Applicant's proposed name as follows:

The proposed name, (b) (4) is unacceptable because (b) (4)

(b) (4)

Use of these stems in proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are

similar to established names, thus increasing the chance of confusion among those drugs. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names. We recommend you withdraw the name and submit a request for review of the alternate proposed proprietary name, Suclear.

The presence of the (b) (4) stem, increases the phonetic similarity of (b) (4) and (b) (4) and may result in confusion during the drug use process.

Additionally, the proposed product contains multiple active ingredients, however only one of the ingredients "PEG" is identified in the proposed name, (b) (4) thereby making the name misleading. This name could also result in confusion because healthcare practitioners may believe that only PEG is contained in the product.

Braintree inquired if they could withdraw the name (b) (4) and ask for the alternate name Suclear be reviewed by DMEPA. DMEPA agreed and Braintree will submit a formal letter by the end of the week.

The teleconference ended cordially.

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/s/

NITIN M PATEL
06/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595

INFORMATION REQUEST

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Vice President, Regulatory Affairs
60 Columbian Street West
PO Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350 and (b) (4) Oral Solution.

We are reviewing the clinical and statistics sections of your submission, as well as your request for a (b) (4) waiver of pediatric studies, and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Clarify whether or not elements that constituted protocol violations were prespecified in protocols for studies 301 and 302. If they were, provide the elements that constituted protocol violations in studies 301 and 302.

2. We note that listings for protocol violations are provided in module 5, listing 16.2.20 for studies 301 and 302. Tabulate all protocol violations provided in the listings for studies 301 and 302, separately by study and violation in the format shown below:

Reason for protocol violations	**N**	**%**
Did not return IP or containers..... Etc.		

3. Explain how you documented vomiting in studies 301 and 302. We note that the treatment questionnaire and symptom scale that were completed by the subjects did not contain a question specifically addressing vomiting or the number of episodes of vomiting.

4. Provide additional explanation for all patients that were considered screen failures when it is stated that they "did not meet criteria". Specify which criteria were not met for all such patients in studies 301 (3 subjects) and 302 (5 subjects).

5. Clarify the definitions of the different populations in studies 301 and 302 and which populations were used for efficacy and safety assessments (i.e., intent-to-treat (ITT), modified intent to treat (mITT), total ITT, subjects treated, subjects in efficacy assessment and safety population). Also, provide the numbers (Ns) in each population. Based on your statistical analysis plan and protocols for each study, it is not clear how populations were defined and which ones were used for efficacy and safety analyses. In addition, for Study 301, explain why six patients in the BLI850 group were excluded from the ITT population after randomization.

6. Provide the literature reference where the original colonoscopy assessment cleansing grade was developed (see table below) rather than reference to previously approved products and cleansing grades previously used.

Colonoscopist Colon Cleansing Score

Score	Grade	Description
1	Poor	Large amounts of fecal residue, additional cleansing required
2	Fair	Enough feces or fluid to prevent a completely reliable exam
3	Good	Small amounts of feces or fluid not interfering with exam
4	Excellent	No more than small bits of adherent feces/fluid

Source: Table 301-1, Protocol Number BLI850-301, page 22

7. Based on the clinical study reports, the analysis of abnormal shifts among patients with normal baseline laboratory parameters (BLI850-301: Table 301-21, page 52; BLI850-302: Table 302-20, page 54) appears to be limited to patients without a missing value on any of the laboratory parameters. For both trials, provide revised Tables, where, for each laboratory parameter, the analysis is limited to patients without missing data only for that specific parameter.

8. Repeat the analyses requested in item 7, above, separately for the age subgroup <65 and ≥ 65, as well as for the patients that are and are not considered high-risk. High risk patients are those that reportedly had a medical history of cardiac, renal or vascular problems (hypertension), or diabetes.

9. Provide the program code used to generate Tables 301-21 and Table 302-20, as well as for the analyses requested in items 7 and 8, above.

10. Provide a revised laboratory dataset that includes the following variables: an indicator for whether the patient is included in the intention-to-treat analysis, randomized treatment, treatment received, high-risk group, and an indicator for whether the baseline assessment is within the normal range.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge your request for a (b) (4) waiver of pediatric studies in patients 0 through 16 years of age because (b) (4)

We do not agree that you meet the criteria for a (b) (4) waiver. (b) (4)

See Draft Guidance for Industry, How to Comply with Pediatric Research Equity Act.

For these reasons, we do not agree with your request for a (b) (4) waiver. We may agree to a partial waiver in birth to less than (b) (4) of age because the product fails to represent a meaningful therapeutic benefit over existing therapies for this group and is unlikely to be used in a substantial number of pediatric patients in this age group because bowel preparation can be achieved by administering clear liquids for 24 hours to these patients.

If you decide to request a partial waiver for birth to less than (b) (4) of age and a deferral for (b) (4) years of age, we suggest that you take the below comments into consideration when you submit the pediatric plan. The plan must fulfill the requirements as per section 505B of the Federal Food Drug and Cosmetic Act, including a timeline for completion of pediatric studies as described below. A pediatric plan is a statement of intent that outlines the pediatric studies sufficient to demonstrate dose, safety, and efficacy. The pediatric plan must contain a timeline for the completion of pediatric studies, i.e., the dates of (1) protocol submission, (2) study completion and (3) submission of study reports. In addition, you must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

When developing your pediatric plan consider the following:

1. We may be willing to extrapolate efficacy for this indication and product. If your development program will rely on extrapolation of efficacy from adequate and well controlled studies in adults, you must include data to support the extrapolation, as well as the plans for the supportive studies to support dosing and safety.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf

2. Your pediatric plan should include a dose-finding study and a short term study to evaluate the safety and efficacy of the product for the claimed indications in all relevant pediatric subpopulations, paying particular attention to electrolyte abnormalities and potential neuropsychiatric events associated with PEG 3350.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity, consult with the Division of Gastroenterology and Inborn Errors Products. Note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
05/10/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Braintree Laboratories, Inc
60 Columbian Street West
P.O.Box 850929
Braintree, MA 02185

ATTENTION: Vivian A. Caballero
Vice President, Regulatory Affairs

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate Oral Solution and PEG-3350, Sodium Bicarbonate, Sodium Chloride, Potassium Chloride for Oral Solution.

We also refer to your February 14, 2012, correspondence, received February 15, 2012, requesting review of your proposed proprietary name, (b) (4) We have completed our review of the proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

We note that you have not proposed an alternate proprietary name in your submission dated February 14, 2012. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Scherer at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/04/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595

FILING COMMUNICATION

Braintree Laboratories, Inc.
Attention: Vivian Caballero
Vice President, Regulatory Affairs
60 Columbian Street West
PO Box 850929
Braintree, MA 02185

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated December 16, 2011, received December 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350 and (b) (4) Oral Solution.

We also refer to your amendments dated January 10, January 24 and February 14, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 19, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 21, 2012.

During our filing review of your application, we identified the following potential review issues:

1. It is unclear if you have appropriately addressed the combination rule, i.e., established that each component makes a contribution to the claimed effect (see 21 CFR 300.50).

2. You have not provided clear justification of the 15% non-inferiority margin used in the analysis of the primary efficacy endpoint.[1] Your choice of a non-inferiority margin should be supported by analyses based on historical studies of the active control. The non-inferiority margin of 15% may not be considered acceptable.

3. We acknowledge your request for a waiver of PREA studies. Your justification for a (b) (4) waiver of PREA studies may not be acceptable.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Submit a copy of the Letter of Authorization (LOA) to reference DMF (b) (4) for PEG 3350 ((b) (4)

2. (b) (4) DMF (b) (4) which you have referenced is not available for review. Verify that you have provided the correct DMF number and submit a new LOA.

3. Address the drug-drug interaction potential between the components of the formulation (i.e., oral sulfates and PEG-ELS).

4. Provide the complete study report including datasets and analytical validation/assay reports for the following published study titled: "Clinical trial: Single- and multiple-dose pharmacokinetics of polyethylene glycol (PEG-3350) in healthy young and elderly subjects" (R.W. Pelham et al, Alimentary Pharmacology & Therapeutics, 2008 [Braintree trial]).

5. We acknowledge that you have submitted datasets. However, the primary endpoint (cleansing success) and the related SAS programs were not included. You should provide the following information for Studies BLI850-301 and BLI850-302.

   i) New datasets in electronic format consistent with the FDA Data Specifications document: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm). Note that adherence to CDISC standards are recommended but not required. The dataset you provide should include the following variables:

      Study number;
      Investigator site (Site in your submission);
      Patient number/name (PT in your submission);
      Treatment name;

[1] Please reference the following FDA Guidance for Industry:
www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf

Intent-to-treat population (Yes or No) - ITT;
Modified Intent-to-treat population (Yes or No) - mITT;
Per Protocol population (Yes or No) - PP;
Patient used in the primary analysis (Yes or No);
Patient used in the secondary analysis (Yes or No);
Gender;
Age (year);
Race;
Weight (kg);
Colon cleansing assessment using a four point scores (from 1 to 4) - Bowel preparation grade in your submission;
Cleansing success (Yes for point scores 3 and 4; NO for point scores 1 and 2);
Adequacy of cleaning (Yes for cleaning adequate; otherwise NO);
Need for re-preparation (Yes or NO);
Number of excellent preparations as graded by the blinded colonoscopist;
Number of examinations in which the colonoscopist reached the cecum;
Was exam completed?
If the exam was not completed, provide the reason;

ii) In addition, for Study# BLI850-301, submit well-commented SAS programs used to generate Tables 301-4, 301-5, 301-6, and 301-7. For Study# BLI850-302, submit SAS programs used to generate Tables 302-4, 302-5, 302-6, and 302-7.

Modify your submitted programs so that they are able to input data from the dataset requested in item *i)* above. If necessary, add additional variables needed for this dataset so that the modified SAS programs can successfully create the tables listed in item *ii)* above.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a (b) (4) waiver of pediatric studies for this application. While the proposed waiver is currently under review, we note that it is unlikely we will grant a (b) (4) waiver of pediatric studies for the following reasons:

(b) (4)

Once we have fully reviewed your request, we will notify you if the (b) (4) waiver request is denied and a pediatric drug development plan is required. If the (b) (4) waiver request is denied, you will need to submit (1) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (2) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this application.

If you have any questions, call Matthew Scherer, Senior Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, MD, FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
03/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203595

NDA ACKNOWLEDGMENT

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

Dear Ms. Caballero:

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

Name of Drug Product: [redacted] (b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate, polyethylene glycol 3350 and [redacted] (b) (4) Oral Solution

Date of Application: December 16, 2011

Date of Receipt: December 19, 2011

Our Reference Number: NDA 203595

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and

reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 203595** submitted on December 16, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not

obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MATTHEW C SCHERER
01/09/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203595 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Suclear Established/Proper Name: sodium sulfate, potassium sulfate, and magnesium sulfate & PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride Dosage Form: oral solution and powder for oral solution		Applicant: Braintree Laboratories, Inc. Agent for Applicant (if applicable):
RPM: Matthew Scherer		Division: Division of Gastroenterology and Inborn Errors Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 1-19-13 (target date is 1-18-13)	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

he **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 4 (new combination)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☐ MedGuide w/o REMS
- ☐ REMS not required

Comments:

BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

nswer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA plement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	Included
Documentation of consent/non-consent by officers/employees	Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 1-18-13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Final label submitted 1-16-13
• Original applicant-proposed labeling	Submitted 12-16-11
• Example of class labeling, if applicable	Approved label and MG for Prepopik included

[4] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Final Med Guide and Draft IFU submitted 1-17-13
• Original applicant-proposed labeling	Submitted 12-16-11
• Example of class labeling, if applicable	See Prepopik Medication Guide attached to Prepopik PI (above)
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Carton and 2-Liter bottle labels submitted 1-17-13, 6-ounce bottle label submitted 10-26-12
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	• 9-17-12, 5-4-12 • 9-17-12, 5-3-12 • Other: 7-5-12, 6-29-12
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 9-14-12 ☒ DMPP/PLT (DRISK) 12-14-12, 10-2-12 ☒ ODPD (DDMAC) 11-7-12 ☒ SEALD 1-14-12 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	2-17-12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC August 1, 2012 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	1-4-13 (2), 12-6-12, 10-10-12, 10-3-12 (2), 9-18-12, 9-14-12 (2), 8-24-12, 8-3-12, 7-18-12, 7-6-12, 5-10-12, 3-2-12, 1-9-12
❖ Internal memoranda, telecons, etc.	12-12-12
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	NA
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	1-18-13
Cross-Discipline Team Leader Review *(indicate date for each review)*	1-18-13
PMR/PMC Development Templates *(indicate total number)*	2 FDAAA PMRs
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL review 1-18-13
• Clinical review(s) *(indicate date for each review)*	1-3-13, 2-26-12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 1-3-13 Clinical review (p 29)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	Safety Statistics: 11-5-12, 9-12-12 PMHS: 10-22-12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	 NA NA ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	11-26-12, 9-6-12
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	10-31-12, 2-17-12
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	10-2-12, 9-18-12, 2-7-12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	10-11-2
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10-4-12, 9-14-12, 2-2-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	2-17-12
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	1-17-13, 8-17-12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See 8-17-12 CMC review (p 86)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 3-20-12 See 8-17-12 CMC review (p 86) ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review) See 8-17-12 CMC review (p 7)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's DRA.