# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211281Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 211281

**REFUSAL TO FILE**

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

Dear Ms. Caballero:

Please refer to your New Drug Application (NDA) dated June 29, 2018, received June 29, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for BLI400 (lactitol monohydrate) powder for reconstitution for oral administration, 21 g.

Please also refer to our August 21, 2018, Initial Pediatric Study Plan (iPSP) Written Response letter and your subsequent August 27, 2018 submission to IND 118906 containing a proposed Agreed iPSP.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reason:

> Failure to address the requirements under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) because you have not provided an agreed upon pediatric study plan to conduct studies to assess the safety and effectiveness of your product for treatment of chronic constipation in pediatric patients.

Although you have submitted a proposed Agreed iPSP dated August 27, 2018, you have not adequately addressed all of our comments. We are committed to working with you to reach agreement on your iPSP as expeditiously as possible to facilitate resubmission of your NDA. We note that the proposed Agreed iPSP needs to be reviewed by the Pediatric Review Committee (PeRC) before we can finalize our determination of its adequacy. We will respond within 30 days of receipt of your proposed Agreed iPSP submission as to whether it constitutes an Agreed iPSP.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

1. You are relying on published literature for chronic toxicity, fertility and early embryonic development and genotoxicity studies to support the safety of BLI400. Since you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you or for which you have not obtained a right of reference (e.g., published literature), your marketing application will be a 505(b)(2) application. Upon resubmission of your NDA, you should update the 356h accordingly. You also need to provide an adequate scientific justification to establish that the published literature is scientifically relevant to your proposed product.

2. You have not provided clear justification of how the available data can preclude the potential effects of lactitol, a new molecular entity (NME), on the QT interval (e.g., TQT study). We note that in your phase 1 trial, lactitol was measurable in plasma, and mean $C_{max}$ was 776 ng/ml under fed condition and 2780 ng/ml under fasted condition following a 21 g dose in healthy subjects. If you believe a thorough QT (TQT) study is not warranted, you should submit a justification with supporting data and a request for TQT study waiver to the IND.

3. Your handling of duplicate patients who enrolled in both Study 301 and Study 302 is unclear. Patients who enrolled in more than one phase 3 study (i.e., Study 301 and Study 302) should be included in the ITT efficacy analysis population only once, corresponding to the first study in which they enrolled. However, patients who enrolled in both studies at the same time (any overlap in study participation dates) should be excluded entirely from both efficacy and safety populations. Accordingly, revise the efficacy analysis of each study, and update the efficacy tables in the clinical study reports and ISE analysis. You should provide a tabular listing of all duplicate patients, and specify the population they were included in and why, to permit verification of the revised results. Include in your response updated datasets that contain a flag for this new efficacy population (i.e., revised m-ITT).

4. Regarding the safety populations, the same approach described in #3 should be applied. Patients should be included in the safety population for only one of the two phase 3 studies, corresponding to the first enrollment. Update the common adverse event tables for the CSRs of Studies 301 and 302 using the same approach. The ISS population should reflect all patients who received at least one dose of study drug. Each individual patient should appear only once in the ISS population, utilizing the phase 3 record associated with the first study (and its extension, if applicable) that the patient enrolled in. Provide a tabular listing of all duplicate patients, which population they were included in (and what record was used where appropriate), and supporting rationale. Include in your response updated datasets that include a flag for the safety population defined as requested (i.e., modified safety population).

5. We note that you appear to be following the option to split the ISS and ISE between modules 2 and 5, rather than providing a stand-alone ISS and ISE. We encourage you to review the Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, and ensure that your submission complies with the recommendations. Specifically, while it is acceptable for the module 5 contents to focus on data tables, it is still necessary to provide sufficient narrative text regarding the methodology and interpretation of the results. The narrative text of the summary of clinical safety (module 2.7.4) is sparse and does not describe in detail the methodology surrounding the ISS. In particular, this section should describe in detail how the analysis population was defined, as well as patient disposition and the handling of duplicate subjects.

6. We note that although your primary and key secondary endpoints for Study 302 appear acceptable and consistent with prior agreements, the purpose of extending the trial duration to 6 months is to assess both safety and long-term efficacy. You should provide additional analyses of efficacy that cover the full 6-month treatment period, and analyses comparing the first 12 weeks to the last 12 weeks, to determine if there is persistence or waning of therapeutic effect/evidence of tachyphylaxis over time. For example, you should explore some of your secondary endpoints past 12 weeks, including:

    a. Bowel movement frequency per week and per month out to 6 months;
    b. Number of doses of rescue medication taken per week and per month, through 6 months; and
    c. Change from baseline in the complete spontaneous bowel movement (CSBM) rate per week, using the last 2 weeks of the trial compared to baseline (week 23-24 data compared to baseline).

7. You should assess the potential for the study drug to cause a rebound effect after withdrawal (for example, how does CSMB rate per week change in the first 1-2 weeks after treatment discontinuation, compared to baseline).

8. We note that you excluded all patients enrolled at site 30/32 due to study site misconduct. Provide additional information such as when the misconduct was detected, what actions were taken to bring the site into compliance, whether the site was terminated while the study was ongoing, and whether this was reported to the IRB or the FDA. Further, clarify whether or not the SAP was amended to alter the primary efficacy analysis population to exclude this site, and if so, if this occurred before or after database lock. Provide sensitivity analyses for the primary and key secondary endpoints including these patients in the analysis population.

9. Similarly, provide additional details regarding the fire that destroyed some study-related records and specify when it occurred, and what data were lost. Provide an explanation for why some safety data are available but all efficacy data were lost.

10. You included in your draft labeling a statement that patients may reduce the dose by 50% if diarrhea occurs. You have not provided adequate data to support an alternate dosing regimen. Provide subgroup analyses of the patients who underwent dose reduction during the trial, including the proportion of patients in the subgroup who were an "overall responder" and key safety analyses (including treatment-emergent adverse event [TEAE] rates, serious adverse event [SAE] rates, diarrhea leading to discontinuation, etc. in patients who required any dose reduction, compared to those who did not, and to those who received placebo). In addition, provide sensitivity analyses of the primary endpoint 1) excluding all patients who dose reduced, and 2) considering them as non-responders.

11. It appears that analyses by racial and ethnic subgroups were not included in clinical study reports for BLI400-301 and BLI400-302. Provide efficacy results for relevant racial and ethnic subgroups for trials BLI400-301 and BLI400-302.

12. We have the following additional comments and questions pertaining to the submitted datasets:

    a. Drug accountability (DA) domain was not submitted for Study 303. If available, include in your resubmission to better inform exposure data.

    b. In Study 302, there are 9 patients (see list below) who appear to have been treated (per information in the custom Diary Assessments ["ZD"] domain) but for whom the safety flag was set to "N." Provide rationale for why these patients, if they received one or more doses of study drug, were excluded from the safety population.
        - BLI400302 (b) (6)
        - BLI400302
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    c. You have not submitted data on bilirubin test results for Study 301. As bilirubin is an important component of the evaluation to assess a drug's potential for hepatoxicity, submit the bilirubin test results, if available. If bilirubin data were not collected, explain why.

13. Given that the proposed dose is 21 g, an unknown impurity of even (b) (4)% would provide an equivalent of (b) (4)mg impurity per dose, which may be significant. Therefore, you must provide the results of stress stability studies on the active pharmaceutical ingredient (API) to assure that unknown impurities are not generated.

    a. The proposed acceptance limits of "for information only" for unknown impurities and unknown degradants in the drug product specification are not in line with the limits

recommended in ICH Q3B. Revise the drug product specification and set the limits for the unknown impurities and unknown degradants according to recommended limits in ICH Q3B.

b. Based on the data generated from the forced-degradation studies (stress stability studies), provide supporting information that shows the proposed refractive index detection is capable of detecting and adequately quantifying unknown impurities and degradation products.

14. Include in your resubmission the electronic datasets in .xpt format for individual plasma concentrations and PK parameters for Study BLI400-101.

15. Section 1.3.5.3 Exclusivity Claim does not request any timeframes or exclusivity. While an exclusivity request is not required, please specify the timeframe and exclusivity that you are requesting.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified high-level content and format issues. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

**PROPOSED PROPRIETARY NAME**

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, contact Andrew Kelleher, Ph.D., Regulatory Project Manager, at (301) 796-9330.

Sincerely yours,

*{See appended electronic signature page}*

Jessica J. Lee, M.D., M.M.Sc.
Associate Director
Division of Gastroenterology and Inborn Errors
Products Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Prescribing Information

10 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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JESSICA J LEE
08/28/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118906

**MEETING MINUTES**

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BLI400 (lactitol) Powder for reconstitution, (b) (4) grams

We also refer to the teleconference between representatives of your firm and the FDA on January 14, 2014. The purpose of the meeting was to discuss the lactitol development program.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | Type B |
| **Meeting Category:** | End of Phase 2 |
| **Meeting Date and Time:** | January 14, 2014, 3:00 to 4:00 pm |
| **Meeting Location:** | White Oak Building 22, Room 1421 |
| **Application Number:** | IND 118906 |
| **Product Name:** | BLI400 (lactitol) Powder for reconstitution |
| **Indication:** | treatment of chronic idiopathic constipation |
| **Sponsor/Applicant Name:** | Braintree Laboratories, Inc. |
| **Meeting Chair:** | Rob Fiorentino |
| **Meeting Recorder:** | Matthew Scherer |

**FDA ATTENDEES**
Donna Griebel, MD, Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, MD, FAAP, CPI, Deputy Director, DGIEP
Robert Fiorentino, MD, Acting Medical Team Leader, DGIEP
Lauren Weintraub, MD, MPH, Medical Officer, DGIEP
Wen-Jen Chen, PhD, Statistician, Division of Biometrics III
Sushanta Chakder, PhD, Supervisory Pharmacologist, DGIEP
Tamal Chakraborti, PhD, Pharmacologist, DGIEP
Marie Kowblansky, PhD, CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Yow-Ming Wang, PhD, Team Leader, Division of Clinical Pharmacology III
Sandhya Apparaju, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology III
Matthew Scherer, MBA, Senior Regulatory Project Manager, DGIEP

**SPONSOR ATTENDEES**
Mark vB. Cleveland, PhD, Senior Vice President, R&D/RA
Vivian Caballero, Vice President, Regulatory Affairs
Russell Pelham, PhD, Director, Pharmacology and Toxicology
James Banschbach, VP Quality and Compliance

## 1. BACKGROUND

Braintree has requested this End of Phase 2 meeting to discuss lactitol for the treatment of chronic idiopathic constipation. The sponsor is proposing to submit an NDA under the 505b2 pathway, relying in published literature studies to support safety and efficacy. Lactitol is a sugar alcohol (D-galactosesorbitol) and acts as an osmotic laxative. It is used in several other countries (not US) as a treatment for hepatic encephalopathy and for constipation.

## 2. DISCUSSION

1) Lactitol has been in worldwide use as a laxative for many years. As reviewed in IND 118,906 (BLI400 Lactitol), Item 9.3, numerous clinical study reports have been published providing information concerning dose, efficacy and safety. These reports will be extensively reviewed in the NDA.

*a) Are the published clinical studies sufficient to support dose recommendations for the phase 3 studies outlined below?*

**FDA Response:**

**Yes, the proposed dose of lactitol appears to be within the range previously assessed in published studies.**

*b) Are these published reports sufficient, in conjunction with successful completion of the studies outlined below, to support a conclusion of safety and efficacy?*

**FDA Response:**
**Under 505(b)(2), an applicant may rely upon data obtained from studies not performed by the applicant and for which the applicant does not have the right of reference for approval of a marketing application. While these data may be considered supportive, none of the published studies of lactitol that you cited represent an adequate, well-controlled clinical trial to evaluate the safety or efficacy of lactitol for treatment of *chronic idiopathic constipation*. In addition, since the raw data from the published clinical studies are not available for review by the Agency, the safety and efficacy results from these studies cannot be validated. Accordingly, the efficacy evidence in support of the study drug BLI400 for the proposed indication will be mainly based upon Study BLI400-301. It will be a review issue to determine whether or not Study BLI400-301 can successfully support BLI400 for the proposed indication.**

**To provide sufficient evidence of effectiveness from the single proposed phase 3 clinical trial, the results will need to be strongly persuasive (i.e., highly statistically significant) and internally consistent. Refer to the FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.[1]**

2) Clinical Study BLI400-301:

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf

The objective of this study is to demonstrate the safety and efficacy of BLI400 (lactitol) in providing treatment for chronic idiopathic constipation. Following a screening period to confirm ROME constipation status, eligible study subjects will be given a 21 g daily dose of lactitol (or a corresponding volume of digestion resistant maltodextrin) for 6 months.

The primary efficacy endpoint is the proportion of subjects who are weekly responders for 9 out of the first 12 weeks, with at least 3 of these weeks occurring in weeks 9 - 12. Secondary efficacy endpoints include the percent of patients not meeting ROME criteria during each study week.

Responder definitions will be based on weekly assessments of complete spontaneous bowel movements (CSBMs). A weekly responder will be defined as a subject who has an average of $\geq$ 3 CSBMs/week and an average increase from baseline of > 1 CSBM/week for that week.

*Is the primary endpoint adequate to support a drug indication and claim of treatment of chronic idiopathic constipation with an overall use period of 12 weeks?*

**FDA Response:**

**The proposed primary endpoint appears acceptable.**

3) Subjects will be provided with rescue bisacodyl for use if they have not had a bowel movement in 4 days or are experiencing significant discomfort from their constipation.
Use of bisacodyl is allowed with the following conditions/restrictions:

- Subjects will be dispensed twenty-five 5mg bisacodyl tablets at each study visit to allow for rescue laxation during the 30 day period between visits. Rescue bisacodyl will be collected at each visit for accountability purposes and will not be re-dispensed. A new set of 25 bisacodyl tablets will be dispensed, ensuring that a subject does not have more than 25 tablets at a given time.

- If a subject does not have a bowel movement within 24 hours of taking a 10mg bisacodyl dose, subjects will be instructed to take a second dose. If after the second bisacodyl dose the subject does not have a BM within 24 hours, the subject will be instructed to contact the site. The investigator will be instructed to consider having the subject return for an evaluation and/or discontinuing the subject from the study.

- Subjects will be instructed to take no more than 30mg of bisacodyl per week. Investigators will be instructed to consider discontinuing subjects that consistently take in excess of the 30mg maximum of bisacodyl per week.

When reporting each bowel movement, subjects will be queried for rescue bisacodyl (or other non-study laxative) use. Bowel movements occurring within 24 hours of rescue laxative use will not be counted toward primary or secondary efficacy analyses.

*Is this acceptable?*

**FDA Response:**

**The proposed plan for bisacodyl rescue treatment appears to be adequate.**

4) Follow up visits during the Treatment Period are scheduled for Days 30, 60, 90, 120, 150 and 180. A post-treatment follow up call is scheduled for 2 weeks after the end of treatment to assess any new and ongoing adverse events. Data collected through Day 90 will be used for the primary efficacy analysis.

*Is this level of follow up acceptable?*

**FDA Response:**

**The planned level of follow up appears acceptable from a safety standpoint. However, since you have defined a "treatment responder" by the number of CSBMs per week, data for your primary efficacy analysis should be collected through Day 84 (12 weeks).**

Clinical Study BLI400-302:

5) This Phase III study of 200 subjects will evaluate the safety of long term dosing of BLI400 (lactitol) for up to one year. Eligible study subjects who meet ROME criteria will be given a 21 g daily dose of BLI400 for 12 months. Approximately 100 elderly subjects (≥ 65 years of age at screening) will be included in the study population. ECGs and laboratory testing will be performed at baseline and each follow-up visit. Adverse event data will be collected through completion of the study.

*Is the study sufficient to demonstrate the long term safety of BLI400 (lactitol)?*

**FDA Response:**

**Based on the guidelines in ICH E1, "The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions," the proposed study duration may be adequate, provided the drug data base adequately characterizes and quantifies the safety profile of lactitol. If adverse events differ between studies BLI400-301 and BLI400-302, it may be more difficult to assess the causality relationship between adverse events observed and the test drug since study BLI400-302 lacks a concurrent control.[2]**

6) In the two Phase III studies described above, up to 600 patients will be exposed to BLI400 (lactitol) for six months and up to 200 patients will be exposed for 1 year

[2] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

(including 100 elderly). Additional experience published in the literature will be reviewed.

*Is this sufficient to demonstrate safety and efficacy?*

**FDA Response:**

**See responses to Questions 1 and 5.**

7) Pharmacology and Toxicology

A BLI400 New Drug Application (NDA) will rely on the extensive published and non-published pharmacology and toxicology data derived from the literature presented in IND 118,906 (BLI400 Lactitol). As stated in Item 4.23 of that IND, detailed toxicology studies were conducted on lactitol and published as reviewed in Item 8.1. They represent a full complement of the types of studies that are usually required as NDA-enabling for an indication such as chronic idiopathic constipation. Studies covering mutagenicity, acute and chronic toxicity, and carcinogenicity effects as well as a complete reproductive toxicology series, were presented and reviewed.

Dr. Fred Reno assessed the design of the most critical toxicology studies in Item 10.1 of the IND and concluded that they were conducted at quality laboratories, were likely conducted under GLP, and that all demonstrated

> "…current knowledge of the state of the art at the time. The studies appear to have been conducted in the early 1990's and reflect what was available as far as regulatory guidelines. ICH guidelines were generally in draft form at this time, but the study designs reflect many of the guidelines available in draft form at the time."

As a result, Braintree believes that there is ample published literature and foreign marketing experience for lactitol to provide significant preclinical and clinical information supporting the safe and effective use of this GRAS compound for treatment of chronic idiopathic constipation, and that further preclinical and toxicology studies are not warranted for this IND or for eventual NDA approval of BLI400.

*Considering the extensive literature available on the safety of lactitol, and its history in the marketplace in ex-US territories, does FDA agree that additional pharmacology and toxicology studies of BLI400 (lactitol) are not required for this IND or NDA?*

**FDA Response:**

**No, we do not agree. It is not possible for us to independently evaluate the data from the published literature studies. There is inadequate information for us to evaluate the carcinogenicity and reproductive toxicity of lactitol from the published literature studies and are thus not acceptable for the NDA application. Please consider that these are refuse-to-file (RTF) issues. To support the NDA, the following nonclinical studies will be required.**

1. **Embryofetal development studies in rats and rabbits and pre and postnatal development study in rats. The reports of these studies must be submitted to the NDA for our review.**

2. **Two-year carcinogenicity studies in mice and rats, or a two-year carcinogenicity study in rats and a 26-week carcinogenicity study in CB6F1-TgHras2 mice as an alternative to a 2-year carcinogenicity study in mice. You need to initiate the 2-year carcinogenicity study in rats before the submission of the NDA and the dose selection protocols (recommended to be submitted as Special Protocol Assessment requests[3],[4]) should be submitted as soon as possible to the Agency. If you choose to conduct the 26-week CB6F1-TgHras2 study in mice instead of the 2-year bioassay in mice as mentioned above, the report of this study needs to be submitted to the NDA for our review.**

8) New Chemical Entity Status. Since lactitol has not been marketed in the US, we submit that it qualifies for New Chemical Entity Status.

*Does FDA agree that lactitol qualifies as a New Chemical Entity?*

**FDA Response:**

**According to 21 CFR 314.108, a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Food, Drug, and Cosmetic Act, is considered a new chemical entity.**

9) We intend the NDA filing to be a 505(b)(2) application, since one or more of the investigations that we will rely upon for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C.355(b)(2)).

*Does FDA agree that lactitol qualifies for a 505(b)(2) application?*

**FDA Response:**

**See response to Question 1. Also, refer to the detailed 505(b)(2) Regulatory Pathway information provided at the end of this document.**

10) The levels of (b) (4) and lactose that are present in the drug substance are less than those that are considered potentially to cause allergic reactions in susceptible individuals.

*Does FDA agree that the drug product with the specifications set out in the IND would not be contraindicated in people who are allergic or sensitive to* (b) (4) *and lactose?*

[3] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080571.pdf
[4] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078924.pdf

**FDA Response:**

**Based on the specifications provided in section 7.1 S.4.1 of the IND application (page 7-7), the amount of lactose in the lactitol drug product will likely be tolerated by patients with lactose intolerance, provided that (b) (4) make up NMT (b) (4)% of the drug substance, as proposed in the specification; this would be equivalent to (b) (4) mg lactose/ (b) (4) grams lactitol.[1] Please note that while this quantity of lactose is acceptable for most patients with lactose intolerance, there is wide variability in degree of tolerance among individuals with this condition. Furthermore, any lactose-containing product should not be administered to patients with rare hereditary problems of severe congenital lactase deficiency, galactose intolerance, or glucose-galactose malabsorption.**

**However, for patients with (b) (4) allergy or intolerance, the risk of exposure to these substances (i.e., (b) (4)) may constitute a contraindication for use of a particular medication. Since you have not provided information regarding the expected amount of (b) (4) in your finished drug product, we cannot comment.**

*Reference: U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality. (2010). Lactose intolerance and health (NIH Publication No. 10-E004).*

*Meeting Discussion*

(b) (4)

*Braintree notes that the USP monograph for lactitol does not contain a specification for (b) (4) Braintree intends to use a lactitol drug substance with a (b) (4) specification of NMT (b) (4)ppm (consistent with the E.P. Monograph for (b) (4)). FDA agrees with this approach.*

**Additional comments from the FDA**

1. **You have specified that the "maltodextrin utilized as the placebo in Study BLI400-301 will be digestion-resistant maltodextrin." Digestion-resistant maltodextrin is soluble corn fiber, which is the fiber ingredient in Fibersol®, a dietary fiber supplement which can affect stool frequency and consistency. The recommended serving size of Fibersol® is 2.8 or 5.6 grams, which is lower than the proposed dose for your placebo. Use of dietary fiber as the placebo in your pivotal clinical trial of lactitol for patients with chronic idiopathic constipation may impact efficacy. Consider selecting an alternative substance as your placebo.**

*Meeting Discussion*

*Braintree clarifies that it will use "regular" (i.e., not digestion-resistant) maltodextrin for the clinical trials. FDA agrees with this approach.*

2. **We have identified the geriatric population as a group which may derive particular benefit from the introduction of lactitol to the U.S. market. Therefore, we recommend that you obtain sufficient placebo-controlled data for geriatric labeling of lactitol by ensuring enrollment of adequate numbers of patients ≥ ages 65 and 75 in Study BLI400-301, per CFR 201.57(c)(9)(v). Please refer to the Guidance for Industry: Content and Format of Geriatric Labeling.[5]**

3. **Please address the following comments regarding Study BLI400-301:**

   - **Your proposed one-sided significance level of 0.05 for the sample size calculation and statistical testing is not acceptable. If you plan to conduct one pivotal study for the efficacy assessment, in order to demonstrate a persuasive treatment effect of the study drug, the study Type I error rate should be much smaller than 0.025 (e.g., 0.001; see response to question 1b).**
   - **Specify the secondary endpoints intended for labeling. Moreover, you should propose a multiplicity adjustment method to control the overall Type I error rate in a strong sense for the primary and the secondary endpoints comparisons.**
   - **Submit the final protocol and draft SAP to the Agency for review prior to the trial initiation since changes to the statistical analysis plan after the start of study may compromise the interpretation of the results and/or raise significant review concerns.**

4. **Please address the following clinical pharmacology recommendations:**

   - **Bioavailability of lactitol should be assessed in a subset of clinical trial patients using rich PK sampling.**
   - **The NDA should address the effect of food on the absorption/PK of lactitol.**
   - **We recommend that you allow patients with renal or hepatic impairment to be enrolled in the planned clinical trials, in order to understand safety of lactitol in these subgroups.**

5. **Lactic acidosis, though rare, has been identified as a potential serious adverse effect of osmotic laxatives, particularly in the elderly population. Therefore, your protocol should include plans to evaluate for lactic acidosis if a patient's safety laboratory studies reveal a low serum bicarbonate level with anion gap.**

[5] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075062.pdf

## 3. ADDITIONAL COMMENTS

### PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

### DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

### 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also

include that information in the cover letter for your marketing application in a table similar to the one below.

| **List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature** | |
|---|---|
| **Source of information (e.g., published literature, name of listed drug)** | **Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)** |
| *1. Example: Published literature* | *Nonclinical toxicology* |
| *2. Example: NDA XXXXXX "TRADENAME"* | *Previous finding of effectiveness for indication X* |
| *3. Example: NDA YYYYYY "TRADENAME"* | *Previous finding of safety for Carcinogenicity, labeling section XXX* |
| *4.* | |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

## 4. ISSUES REQUIRING FURTHER DISCUSSION

None

## 5. ACTION ITEMS

None

## 6. ATTACHMENTS AND HANDOUTS

None

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MATTHEW C SCHERER
01/21/2014