CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209376Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Pre-NDA 209376

MEETING MINUTES

Luitpold Pharmaceuticals, Inc.
Attention: Marsha Simon
Senior Manager, Regulator Affairs
800 Adams Avenue
Norristown, PA 19403

Dear Ms. Simon:

Please refer to your Pre- New Drug Application (Pre-NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Multitrace (Trace Elements Injection).

We also refer to the teleconference between representatives of your firm and the FDA on August 3, 2016. The purpose of the meeting was to agree on submission of admixture protocols, understanding of "narrative summary data" for submission of the application and discuss section 14 of the labeling section for the submission.

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 (240) 402-8689.

Sincerely,

{See appended electronic signature page}

Jacqueline LeeHoffman, Pharm.D.
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 C
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 3, 2016, 11:00 PM – 12:00 PM ET
Meeting Location:	Teleconference
Application Number:	Pre-NDA 209376
Product Name:	Multitrace (Trace Elements Injection)
Indication:	trace element additives to parenteral nutrition
Sponsor/Applicant Name:	Luitpold Pharmaceuticals, Inc.
Meeting Chair:	Stephanie Omokaro, MD Joette Meyer, Pharm.D.
Meeting Recorder:	Jacqueline LeeHoffman, Pharm.D.

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Error Products (DGIEP)
Dragos Roman, M.D., Associate Director, DGIEP
Joyce Korvick, M.D., Deputy Director for Safety, DGIEP
Stephanie O. Omokaro, M.D., Clinical Team Leader, DGIEP
Joette Meyer, Pharm.D., Associate Director for Labeling, DGIEP
Joel L. Weissfeld, MD MPH, Medical Officer, Division of Epidemiology I, Office of Surveillance and Epidemiology
Dina Zand, M.D., Clinical Reviewer, DGIEP
Elizabeth Hart, M.D., Clinical Reviewer, DGIEP
Omolara Adewuni, M.D., Clinical Reviewer, DGIEP
David Joseph, Ph.D., Supervisor Pharmacologist/Toxicologist, DGIEP
Fang Cai, Ph.D., Pharmacologist/Toxicologist, DGIEP
Yeh-Fong Chen, Ph.D., Team Leader, Statistical Reviewer, Division of Biometrics III
Kevin Bugin, M.S. Project Manager Supervisor, DGIEP
Danuta Gromek-Woods, Ph.D. Chemist, Office of Product Quality (OPQ)
Martin Haber, Ph.D., Chemist, Office of Product Quality (OPQ)
Jeffrey Trunzo, RPh, MBA, Office of Unapproved Drug and Labeling Compliance OUDLC
Barbara Wise, Ph.D., RN, CPNP, Team Leader, OUDLC
Carolyn Yancey, M.D., Medical Officer, DPMH
Elizabeth Shang, Ph.D., R.ph., Reviewer, Division of Clinical Pharmacology III

Maria Walsh, R.N., M.S.N., Associate Director for Regulatory Affairs, Office of Drug Evaluation III (ODEIII)
Richard (Wesley) Ishihara, Regulatory Scientist, ODE III
Sue Chih Lee, Ph.D., Team Leader, Division of Clinical Pharmacology III
Tien-Mien (Albert) Chen, Ph.D., Acting Biopharm Lead, Division of Biopharmaceutics
Lisa Shelton, Ph.D., Microbiologist, Division of Biopharmaceutics
Robert Kosko, Jr., Pharm.D., M.P.H., Senior Program Management Officer, Drug Shortage

SPONSOR ATTENDEES

Gopal Anyarambhatla, VP, Research and Development Richard Lawrence, Director of Research and Development
Linda M. Mundy, M.D., Ph.D., FACP, Senior Medical Director
Anna Shurshalina, M.D., Ph.D., Associate Medical Director
Marsha E. Simon, Sr. Manager, Regulatory Affairs
(b) (4)
Ken Thompson, D.V.M., Ph.D., Head of Preclinical Development
(b) (4)

1.0 BACKGROUND

The sponsor is proposing Multitrace® application submission with changes to currently available as unapproved products in the US market in past 29 years. Multitrace is used as additives to Parenteral nutrition and it consist of zinc, copper, manganese and selenium. (b) (4)

The sponsor has pre IND meetings with the division on November 12, 2014 to discuss a full description of the manufacturing process, synthesis, characterization procedures, and API stability data for Zinc Sulfate Heptahydrate, Cupric Sulfate Pentahydrate, Manganese Sulfate Monohydrate, (b) (4), and Selenious Acid concurrent with the finished product.

On September 1, 2015, the sponsor and the division discussed Justification of drug product pH range for the Multi-Element products and elemental impurities limits for the drug product during teleconference meeting.

FDA sent Preliminary Comments to Luitpold Pharmaceuticals, Inc. on August 1, 2016.

2. DISCUSSION

FDA General Comments:

Your planned submission for a multi-element new drug application (NDA) will trigger a requirement for a full pediatric assessment under the Pediatric Research Equity Act (PREA) for all pediatric patients from birth to less than 17 years of age. Your planned

NDA is subject to PREA requirements because the active ingredients have not previously been approved for the proposed indication. Since you are not planning to conduct any clinical studies, you must submit an initial pediatric study plan (iPSP) no later than 210 calendar days before the planned multi-element NDA submission. Do not submit your NDA until agreement has been reached on the iPSP. Failure to include an agreed iPSP with your NDA submission is a potential refuse-to-file issue. The iPSP should include the following:

- **Any requests for deferral, partial waiver, or waiver of pediatric assessments in specific pediatric age groups, if applicable, along with any supporting information to justify your requests;**
- **Details about whether the formulation being developed can be used for all pediatric populations. Otherwise, the iPSP should provide details about any plans to develop a pediatric-specific formulation;**
- **The scientific rationale for the proposed dosing in all pediatric age groups;**
- **A brief summary of relevant non-clinical data to support product use in all pediatric age groups;**
- **A high-level summary of the clinical literature you plan to use to support the safety and efficacy of your product in pediatric patients.**

If available, include a summary of the most recent agreed pediatric investigation with other regulatory agencies, highlighting and commenting on any differences with the iPSP submitted to FDA. Please refer to FDA's March 2016 Guidance for Industry for further details about the content of and process for submitting iPSPs.[1]

(b) (4)

2.1 Chemistry Manufacturing and Control (CMC)

Question 1:

During our PIND meeting on September 1, 2015, the FDA raised concerns that the proposed pH acceptance criteria of 1.5 – 3.5 for Multi-Elements may not be suitable for an injectable dosage form. We reviewed the USP pH limits and in- process pH limits for the following Multi-Element and single entity trace elements:

Table 8. pH Acceptance Criteria

Drug Product	*Fill size*	*Container*	*USP pH limit*	*In-process pH limit*
Mult-Element	*1 mL*	*2 mL vial*	*1.5 to 3.5*	(b) (4)

[1] March 8, 2016 Guidance for Industry. Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm360507.pdf; accessed July 19, 2016.

(b) (4)

(b) (4)

We find that the proposed pH limits 1.5 to 3.5 are consistent with its USP specifications and those of marketed drug products, Addemel N, Zinc Chloride Injection, USP, Cupric Chloride Injection, USP and Chromic Chloride Injection, USP. In addition, the drug product is not for direct injection. It is indicated for use as an additive for intravenous solutions given for Parenteral Nutrition.

Does the above justification address the Agency's concerns?

FDA Response to Question 1:

The justification provided to support the proposed pH limits of 1.5 to 3.5 appears reasonable.

The product carton labeling statement should include: "the product is not for direct injection".

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

Question 2:

Our proposed limits for elemental impurities are as follows

(b) (4)

The Limits for (b) (4) *in the drug product are proposed at* (b) (4) *of ICH parenteral PDE limit. For elements not listed in ICH guidance these limits are under evaluation as process impurities and/or as part of the drug product's container/closure compatibility protocol.*

(b) (4)*, are common leachable elemental impurities from the drug products'* (b) (4) *glass vials. In regard to toxicity, ICH Guideline Q3D Elemental Impurities does not require testing nor provides PDE limits for* (b) (4) *By this guideline* (b) (4) *are classified as "Other elements" and their presence in the drug product must comply with cGMP requirements.*

(b) (4)

(b) (4)

Are proposed Limits for elemental impurities acceptable?

FDA Response to Question 2:

Your proposed limits for (b) (4) **in the drug products are acceptable for your intended dose volume of 1 mL/day, in terms of ICH Q3D.**

(b) (4)

The supporting rationale for the proposed limits for (b) (4) **is unacceptable. An acceptable rationale to justify limits for these elements may be based on a parenteral PDE, which can be derived from animal or human studies using the methods described in ICH Q3D. A parenteral PDE equivalent may be derived from the amount of routine daily intake of these elements from food (including dietary intake recommended by U.S. health authorities), water, and air. Extrapolation from the maximum daily intake as recommended by health authorities (e.g. EPA Reference Dose, ATSDR Minimal Risk Level for chronic use) to generate a parenteral PDE equivalent may also be acceptable. To support these approaches, you must provide detailed information that includes the amount of absorbed element from the oral or inhalation routes of exposure, and full articles for the supporting references.**

Your rationale for supporting the proposed limit for (b) (4) is also unacceptable because the product in the FDA Inactive Ingredient Database that you cited is approved for an acute, life-threatening indication, for which only a single administration is expected, whereas your products may be given chronically. You need to provide a supporting rationale for your proposed (b) (4) limit, as we requested above for (b) (4)

In addition to the elemental impurities that you intend to specify, you also need to conduct a risk assessment for (b) (4), as recommended for parenteral products in ICH guidance Q3D. Specification limits may be needed for these elements, depending on the outcome of your risk assessment (see ICH Q3D for details).

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

Question 3:

The drug product is indicated for use as a supplement to intravenous solutions given for parenteral nutrition. Administration of the solution in parenteral nutrition solutions helps to maintain plasma levels of zinc, copper, manganese, selenium (b) (4) and to prevent depletion of endogenous stores of these trace elements and subsequent deficiency symptoms.

As part of the NDA, Luitpold will perform compatibility studies to demonstrate the compatibility of the product to common parenteral nutrition solutions:

1. Kabiven (amino acids, electrolytes, dextrose and lipid injectable emulsion), for intravenous use.
2. Clinimix E (amino acids with electrolytes in dextrose with calcium) Injections.

1 mL of Multi-Element (Trace Elements Injection, USP) will be added to separate 2 liter IV infusion bags of Kabiven and/or Clinimix E. Samples will be stored under refrigeration (2-8°C) and controlled room temperature (25°C ± 2°C) for 7 days, with testing performed at initial, 24 hours, 48 hours, 72 hours and 7 days. The testing will be performed for Appearance, pH, assay for Zinc, Copper, Manganese, and Selenium.

In addition, the admixtures described above will be inoculated with 10 – 100 CFU of the five (5) USP challenge organisms (e.g. Candida albicans, Escherichia coli, Aspergillus brasiliensis, Pseudomonas aeruginosa, and Staphylococcus aureus).

Samples will be stored under refrigeration (2-8°C) and controlled room temperature (25°C ± 2°C) for 7 days, with viable counts performed on each inoculum at initial and the inoculated samples at initial, 24 hours, 48 hours, 72 hours and 7 days.

Are our proposed admixture studies acceptable?

FDA Response to Question 3:

Your proposed studies are reasonable. Also, determine if the addition of the acidic trace element solutions (pH 2.0) causes a pH change by measuring the pH of the parenteral nutrition solution before and after the addition.

Kabiven is supplied as a 3-chamber container. According to the product labeling, trace elements are added after the bag is activated (i.e., the seals between the containers are broken and the contents mixed). Given that Kabiven contains lipid emulsion, which can obscure an assessment of precipitation, provide additional information on how admixture compatibility will be assessed.

From a sterility assurance perspective, the proposed microbial challenge study is acceptable. For the NDA submission, the rationale for the study design should be provided, including justification for the test storage conditions to support the proposed labeling for the subject product, as well as intended admixture preparation and storage conditions prior to administration. Please include a description of the test methods employed and controls performed. Please include positive controls that demonstrate viability of the challenge organisms over the duration of the test period.

The proposed Prescribing Information (PI) for the Multi-Element and individual trace element products will need to include information on admixture dose preparation and storage conditions and stability after admixing with parenteral nutrition solutions (Section 2, Dosage and Administration, and Section 16, How Supplied/Storage and Handling).

Discussion:

Luitpold agrees with the Agency's response. Prior to filing the NDA, Luitpold plans to submit the admixture protocols with the request for review and comment within 60 days. FDA agreed this approach is acceptable and OPQ agreed to provide comments within 60 days of receiving the protocols.

2.2 Clinical

Question 4:

Luitpold will utilize efficacy data generated from book chapters, oral recommended daily allowance (RDA) with bioavailability guidance recommendations to calculate estimated daily parenteral additive dosing, published literature identified within and beyond the systematic reviews, and societal recommendations such as those from the ASPEN to support the indication in the adult and pediatric population for our NDA submissions for Multi-Element (b) (4) *. The totality of evidence*

will support an indication for the addition of trace elements in parental nutrition for adult populations. Does the FDA agree?

FDA Response to Question 4:

In principle, we agree with your proposal to use the totality of evidence by integrating efficacy information from multiple sources to support the indication for each trace element. In addition to providing the publications identified in the systematic review in the NDA, we request you also provide the primary source publications for any data used to support dosing recommendations including bioavailability data, described in book chapters or review articles. A decision as to whether the totality of the evidence supports the indication and the dosage recommendations will be determined during our NDA review. Refer to the General Comments with regards to the pediatric population.

We have the following specific comments:

- **You plan on including recommendations from Societies, such as those from ASPEN. If other guidelines are available, please provide a discussion on any points of uncertainty or controversy between the guidelines and Society recommendations, with regards to best practices.**

- **Please provide primary references to support the ASPEN guidelines for the individual elements. For some of the elements (e.g., zinc), the recommendations may not have changed substantially since 1979, and for others the recommendations have changed over time. Please provide more complete details as to etiology of the original recommendations and/or the source data to support the more recent changes in the recommendations.**

- **For selenium, the majority of the articles identified in the systematic review used doses higher than the proposed recommended dosage for use in parenteral nutrition. Please provide additional primary data from other routes of administration (e.g., oral) that will support the recommended dose for patients on parenteral nutrition. Also provide bioavailability information and its source data on how oral doses correspond to intravenous doses.**

- **For manganese, we acknowledge your statement that there is a paucity of data for naturally occurring manganese deficiency. Any additional evidence describing the specific clinical effects of manganese deficiency, and at what level this may occur, would be useful to support the proposed manganese dose.**

- **For some of the trace elements:**

Dosing adjustments are recommended in patients with various disease conditions (e.g., increased dose of copper in patients with diarrhea or excessive fluid losses and decreased dose in patients with hepatic or biliary disease). Please include primary source data to support these alternate dosing recommendations for patients with

specific clinical conditions (e.g., burn patients, those with sepsis, those with increased GI losses) or disease states (renal, hepatic impairment) that you plan to include in the Dosage and Administration section of labeling.

There are clinical situations when supplementation may not be needed. For instance, ASPEN supports chromium supplementation only for patients who are on long-term parenteral nutrition without contraindications. These situations must also be addressed in the application and in labeling.

- **Most patients receive parenteral nutrition for a limited period of time and with the anticipation that they will transition to oral nutrition. However, we recognize there is also a smaller cohort of patients who will require chronic parenteral nutrition as their sole source of nutrition. Therefore, you should include in your submission the recommendations for the supplementation needs of these various populations.**

- **We are concerned about recommendations found in your draft labeling for monitoring concentrations of copper (b) (4) in serum or plasma to determine the need for adjustments to the dosage, since (b) (4) copper concentrations in blood do not reflect tissue concentrations of these elements and may not be reliable markers for monitoring the need for supplementation. This concern will need to be addressed appropriately in your planned submission.**

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

Question 5:

Luitpold will utilize the safety data generated from pharmacovigilance (sponsor's PV Works and the Freedom of Information Act) and the published literature within and beyond the systematic reviews to support an indication for the addition of trace elements in parental nutrition for adult populations. Does the FDA agree?

FDA Response to Question 5:

Please clarify how you plan to use PV-Works (pharmacovigilance software system) to generate safety data to support an indication for the addition of trace elements to parenteral nutrition. We have concerns that the available postmarketing data may be confounded and be difficult to interpret. When you submit your application, please provide a narrative summary of the data and discuss the potential causality attribution, organized by individual element.

Regarding use of published literature within and beyond the systematic reviews to support an indication for the addition of trace elements to parenteral nutrition, we recommend you supplement the data in the systematic reviews (which is limited to

intravenous administration for the purposes of parenteral nutrition) with data gained by exposure to the individual trace elements by other routes of administration (e.g., oral). (A framework document will be provided after the scheduled meeting.)

Finally, we are providing the following comment, if you are considering referencing information from a Summary Basis of Approval (SBA) to support your NDA: FDA reviewers' public summaries or advisory committee materials for support of safety and/or effectiveness for a listed drug do not constitute full reports of investigations. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. See 21 C.F.R. 314.430(e)(2). A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug (and not the SBA, FDA reviewers' public summaries or advisory committee materials).

Discussion:

Luitpold requested clarification of 'narrative summary' of the data. FDA explained that a narrative summary is similar to an executive summary and it should summarize the data in full scope including any limitations and conclusions. FDA also clarified that the narrative for each trace element should include all postmarketing data, including both the data obtained through the Luitpold's PV Works and the cases obtained through the Freedom of Information Act.

Question 6:

In the proposed Multi-Element product for adults and pediatric populations, the trace element concentrations in the single-dose 1 mL. vial are zinc (as sulfate) 3 mg, copper (as sulfate) 0.3 mg, selenium (as selenious acid) 60 mcg, and manganese (as sulfate) 55 mcg. (b) (4) *completeness and transparency* (b) (4)*, the concentration of* (b) (4) *will be identified as an impurity* (b) (4) *within each manufactured product. Does the FDA agree with the proposed trace element doses for the Multi-Element product?*

FDA Response to Question 6:

The proposed amounts of zinc, copper, selenium and manganese in the Multi-Element product correspond to the ASPEN 2015 recommended adult daily dosage range for these trace elements. The content of the Multi-Element product appears reasonable. During the NDA review, the team will make a determination as to whether the efficacy and safety data provided in the application are sufficient to support the adult and pediatric recommended dosage ranges. Refer to the General Comments with regards to the pediatric population.

We have the following specific comments:

- **We note your statement in the meeting package that the trace element doses correspond to what you consider to be the lowest effective and highest safe dose to achieve the optimal risk/benefit ratio. Please provide a brief summary in your NDA of the efficacy/safety information you took into consideration when making the determination to select a specific dose from within the recommended range.**

- **The proposed dosing for the Multi-Element product is 1 mL per day for adults (b) (4) In your submission please include a rationale, with supporting data, to support use of the adult dosage in this pediatric, (b) (4) population.**
  - **It appears that the only data you plan to provide for manganese (not as part of a mixture of TE) in pediatric patients is from experience of treating a single patient. Please provide justification on how this limited data will be sufficient to accurately identify the correct dose of manganese in pediatrics.**

- **We agree with your proposal not to include (b) (4) in the Multi-Element product. Regarding the appropriateness of the proposed impurity limit of (b) (4) please see our response to Question #2.**

Discussion:

No additional discussion required. Luitpold agrees with the Agency's response.

Question 7:

(b) (4)

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

2.3 Labeling

Question 8:

There are no adult or pediatric randomized controlled trials (RCT) for (b) (4).
To satisfy the Clinical section, we plan to use controlled studies, when available, or the ASPEN recommendations as the basis for our adult and pediatric dosing regimen. Is this approach acceptable?

FDA Response to Question 8:

According to the labeling regulations (21 CFR 201.57), only adequate and well-controlled studies, as described in §314.126(b), should be described in Section 14 Clinical Studies of the Prescribing Information (PI). The intent is not to discuss all the clinical information that is available.

Discussion:

Lutipold requested input on their proposal to state [redacted] (b) (4) ***in Section 14 of the PI. The FDA agreed with the proposal and noted the details of labeling will be a review issue.***

Question 9:

[redacted] (b) (4) *Does the FDA agree?*

FDA Response to Question 9:

As noted above, only adequate and well-controlled studies should be included in Section 14 Clinical Studies. If you believe that the [redacted] (b) (4) **publication meets the regulatory criteria, you can propose a justification and include a summary of the publication results in Section 14 of the Multi-Element product** [redacted] (b) (4) **As part of the NDA review, we will determine the appropriateness of describing the** [redacted] (b) (4) **data in the PI.**

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

Question 10:

Our pediatric dosing recommendation has been added to Section 2.1 and 8.4.
The use of the adult Multi-Element and four individual Trace Elements for the pediatric, [redacted] (b) (4) *populations are aligned with estimation of need for trace elements. Does the FDA agree?*

FDA Response to Question 10:

Regarding your proposal to use ASPEN recommendations as the basis for pediatric [redacted] (b) (4) **dosing recommendations in the PI, we refer to our response to Questions #4 and #6 above.**

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

Question 11:

This will be the first Multi-Element product with these specific trace elements at these specific doses. For the Clinical, Clinical Pharmacology, Warnings and Precautions, Overdose, and Drug Interactions section of the US Package Insert, Luitpold proposed to reference the best available data from individual element exposure, if not combination trace element exposures, defined as publications by hierarchy of evidence, text books, or ASPEN recommendations. Is this approach acceptable?

FDA Response to Question 11:

We agree with your approach to include a description of relevant safety information on each of the specific trace elements including (zinc, copper, selenium and manganese) in the Warnings and Precautions and Overdosage sections of the PI for the Multi-Trace Element product. Safety information identified in secondary/tertiary references or treatment guidelines should be supported by primary literature data.

See our response to Questions 8 and 9, regarding the type of information to include in the Clinical Studies section.

Information for the Clinical Pharmacology section of the PI (Section 12) should be reported under 12.1 Mechanism of Action and 12.3 Pharmacokinetics. The Mechanism of Action subsection should include a brief summary of what is known about the established mechanism(s) of action of each of the trace elements but does not need to be extensive, as this information is generally understood by clinicians.

The Drug Interactions section (Section 7) should include information only on clinically significant drug interactions. If clinically significant drug interactions are described in the literature, then this section should also include the clinical implications of the interaction and actionable instructions for preventing or managing the interaction.

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

2.4 Regulatory

Question 12:

Luitpold will format the (b) (4) *New Drug Applications (see section xx) following the electronic Common Technical Document (eCTD) requirements for Module 2, Common Technical Document Summaries and Module 5, Clinical Study Reports. As the clinical part of the applications will be primarily supported by published literature with no integrated analyses, the efficacy and safety information can be presented entirely within Modules 2.7.3 and 2.7.4,*

respectively. Thus, Luitpold will not include a separate Integrated Summary of Effectiveness (ISE) or Integrated Summary of Safety (ISS) within Module 5.

Is this approach acceptable?

FDA Response to Question 12:

We request integrated analyses of efficacy and safety for each of the (b) (4) trace elements individually, but we do not expect integrated analyses of safety or efficacy for the elements combined. A separate ISE and ISS within Module 5 may not be necessary, provided the information can be organized logically within Modules 2.7.3 and 2.7.4.

We are providing a proposed framework for how to organize, summarize and tabulate data for each element within the NDA. This document will be sent to you after the scheduled meeting. Please provide us feedback on framework and any other ideas you may have on how to present data for our review.

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

Question 13:

Considering, there will be no new non-clinical and clinical data for the individual trace element presentations, Luitpold will cross reference Module 2, Module 4 and Module 5 sections to the Multi-Element NDA based on proposal under (section 5). Is the approach acceptable?

FDA Response to Question 13:
According to Table 1 in your background package, you plan to cross reference Modules 2, 4 and 5 in the NDAs (b) (4) to the corresponding modules in the Multi-Element NDA. We agree to this approach for all the individual elements except for (b) (4), which is not contained in the Multi-Element product. Therefore, the nonclinical and clinical data for (b) (4) should be included in Modules 2, 4, and 5 of the NDA for that product.

Discussion:

No additional discussion required. Luitpold agreed with the Agency's response.

Additional FDA Comments

1. Fixed Combination Drugs

21 CFR 300.50 states that two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. You must address this requirement in the submission for the Multi-Trace Element product. However, we do not expect that you will need to conduct factorial design studies to address this requirement based on FDA's current thinking as reflected in the proposed rule for fixed-combination and co-packaged drugs published in the Federal Register on 12/23/15 https://www.gpo.gov/fdsys/pkg/FR-2015-12-23/pdf/2015-32246.pdf

2. Pregnant and Lactating Women

Information to support your proposed labeling should reflect the current available knowledge regarding exposure to the trace elements used in your product to accurately inform recommendations for safe use of the product in pregnant and lactating women. As you have proposed various sources of data to support other areas of your application (e.g., RDA guidelines, medical professional society recommendations, pharmacovigilance data, published literature), you should use similar sources to prepare an integrated review and summary of all the information to support your proposed labeling. In addition, consideration should be given to the following:

- **Describe what the anticipated use for these products will be in pregnant and lactating women.**

- **Describe appropriate levels for each element that are required during pregnancy and lactation.**

- **Describe, separately, any known effects of zinc sulfate, copper sulfate, manganese sulfate, chromic chloride, and selenious acid deficiency and toxicity on the following:**
    - **pregnancy outcomes for the mother and fetus (e.g., major congenital malformations, spontaneous abortion, preterm delivery, small-for-gestational age, decreased birth weight, etc.),**
    - **on the breastfed infant,**
    - **on the fertility status of females and males of reproductive potential.**

See "Prescribing Information" below on how to meet the requirements for the Pregnancy and Lactation Labeling Rule (PLLR).

This information in pregnant and lactating women should be incorporated into the efficacy and safety reviews of each individual trace elements in Module 2. Please also make reference to this information in Module 1 with appropriate cross references to Module 2.

3. Electronic Data Submission and Format Requirements

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning May 5, 2017, the following submission types: NDA, ANDA, BLA and Master Files must be submitted in eCTD format. Commercial IND submissions must be submitted in eCTD format beginning May 5, 2018. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

Data extracts:

The overview lists items of information to extract from articles selected for review. These items cover study information, populations studied, interventions, outcomes, and risk of bias. FDA suggests two additional items for data extraction, as follows.

- **To tag articles with information relevant to dose modification, add data fields to enable identification of articles that include special populations, such as, preterm infants, patients with renal impairment, or patients with hepatic dysfunction.**

- **To facilitate safety analysis, map adverse event outcomes to the corresponding MedDRA preferred terms.**

Data submission:

To facilitate FDA review, include items listed below in your NDA.

- **Dates covered by electronic bibliographic database searches.**

- **A listing of articles excluded after review of full text, in standard Reference Manager (RIS) format.**

- **A listing of articles eligible for qualitative synthesis, in standard Reference Manager (RIS) format.**

- **Files containing the data extracted from articles eligible for qualitative synthesis, as comma- separated values (csv), SAS transport (xpt) by study.**

4. Container Closure System

You have not provided details about the container closure system for the products for which you plan to submit marketing applications. We caution you that you will need to provide a detailed safety assessment of all potential leachables for any container closure component (e.g. rubber stopper) that has not been previously used in a FDA-approved drug product. You should contact the Agency to request further guidance on this issue if you intend to use a new component in the container.

Discussion:

No additional discussion required for any of the FDA Additional Comments.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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 Division of Pediatric and Maternal Health 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**.**

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including

the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* 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 related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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, in part, 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, in part, 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, in part, 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*

Reference ID: 4635139

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.

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

/s/

JACQUELINE D LEEHOFFMAN
08/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 123432

MEETING MINUTES

Luitpold Pharmaceuticals, Inc
Attention: Marsha E. Simon
Senior Manager, Regulatory Affairs
800 Adams Avenue
Norristown, PA 19403

Dear Ms. Simon:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Multitrace (trace elements injection).

We also refer to the teleconference between representatives of your firm and the FDA on September 1, 2015. The purpose of the meeting was to discuss the possible filing of a 505(b)(2) New Drug Application(s) for Multitrace® (Trace Elements Injection) product as a modified safer product at a lower dose for use as an additive for total parenteral nutrition (TPN).

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, Senior Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

CDR Matt Brancazio, Pharm.D., MBA
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: C
Meeting Category: Guidance

Meeting Date and Time: September 1, 2015 from 11:00am to 12:00 PM EST
Meeting Location: Teleconference (1-855-828-1770, Meeting ID: (b) (4))

Application Number: 123432
Product Name: Multitrace (trace elements injection)
Indication: **An additive to Total Parenteral Nutrition**
Sponsor/Applicant Name: Luitpold Pharmaceuticals, Inc

Meeting Chair: Wen-Yi Gao, M.D.
Meeting Recorder: CDR Matt Brancazio, Pharm.D., MBA

FDA ATTENDEES
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety, DGIEP
Dragos Roman, M.D., Deputy Director, DGIEP
Wen-Yi Gao, M.D., Medical Officer, DGIEP
Danuta Gromek-Woods, Ph.D., CMC Lead, Office of New Drug Quality Assessment
Robert G. Kosko, Jr., Pharm.D., M.P.H., Senior Regulatory Project Manager, CDER Drug Shortage Program
Christine Bina, Pharm.D., Senior Program Manager, CDER Drug Shortage Program
Peter Chen, R.Ph., Prescription Drug User Fee Staff, Office of Management
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs, Office of Drug Evaluation III
LCDR Wes Ishihara, Regulatory Scientist, Office of Drug Evaluation III
Kevin Bugin, M.S., RAC, Regulatory Health Project Manager, DGIEP

SPONSOR ATTENDEES
Marc Tokars, VP, Clinical Operations
Linda M. Mundy, MD, PhD, FACP, Senior Medical Director
Andy He, PharmD, Manager, Medical Affairs
Gopal Anyarambhatla, VP, Research&Development and Regulatory Affairs
Richard Lawrence, Director of Research and Development
Marsha E. Simon, Sr. Manager, Regualtory Affairs
(b) (4)

(b) (4)

1.0 BACKGROUND

The purpose of this meeting is to discuss the possible filing of a 505(b)(2) New Drug Application(s) for Multitrace® (Trace Elements Injection) product as a modified safer product at a lower dose for use as an additive for total parenteral nutrition (TPN). This product is currently a marketed, unapproved drug for use within the United States and Luitpold is the sole source for Multitrace®. This is the second meeting between Luitpold Pharmaceuticals, Inc. and the Division of Gastroenterology and Inborn Errors Products under PIND 123432. The first meeting, a type B Pre-IND meeting, was held through teleconference on November 12, 2014.

2.0 DISCUSSION

2.1. Regulatory/Clinical

Question 1: *Luitpold believes the literature and scientific rationale for a specific dose in the new formulation (see section 2) will support the approval of* (b) (4) *TPN as a 505(b)(2) application. Does the Division agree?*

FDA Response to Question 1:
If 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., reliance on published literature), then your marketing application will be a 505(b)(2) application. Additionally, you must establish (with scientific rationale) that reliance on the studies described in the literature 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)). Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

We understand that the literature will be the basis of your marketing application; however, the adequacy of the literature presented in your application will be a review issue. We anticipate that this application will go to an Advisory Committee for expert recommendation regarding the adequacy of the literature to support the efficacy and safety of each proposed trace element dose.

We further advise you to submit your literature organized according to route of administration as well as individual trace element. References for any position papers regarding parenteral dosing will need to be submitted as well. Present a table of contents and a framework for the organization of the literature for our review prior to submission of your application. Also include your strategy for summarizing the data and supporting the summary conclusions in succinct fashion.

Meeting Discussion:
The Division acknowledges that the Luitpold may have a Pre-NDA meeting prior to submission of the marketing application and submit the proposed table of contents and framework of the organization of the literature. The Division explained that (b) (4) **could**

Reference ID: 4635139

be submitted at a full user fee application cost whereas the other (b) (4) could be submitted at a half user fee cost if there are no new clinical data and reference to the clinical data in the (b) (4) application. Luitpold plans to reference literature pertaining to products approved or unapproved in support of their (b) (4) application.

2.2. Chemistry, Manufacturing, and Control

Question 2: *At the time of NDA submission, Luitpold proposes to submit six (6) months accelerated stability data (at 40°C/75% RH) and six (6) months long-term stability data (at 25°C/60% RH) for three (3) lots each (b) (4) The twelve (12) months Long-Term stability data (at 25°C/60% RH) for each stability batch will be provided as available during FDA review. All NDA registration lots will be made using a single lot of drug substance (with full CMC data for each API provided within the NDA as no DMFs are available). Proposed stability protocols have been provided to the Agency as part of the briefing package for the meeting. Does the Agency accept this approach?*

FDA Response to Question 2:
Your proposal is acceptable provided that you submit the 12 months long-term stability data for all the registration batches within 3 months from the date of the submission of the original NDA.

Post Meeting Comments:
Sponsors ordinarily may request Fast Track Designation and Rolling Review with a submission to the IND (see guidance for industry, Expedited Programs for Serious Conditions – Drugs and Biologics). However, since you do not have any plans to submit an IND, you may submit this request to a pre-assigned NDA number.

Even if you decide to pursue a Rolling Review submission strategy, you should submit the table of contents and framework for the organization of the literature that you plan to submit (see FDA Response to Question 1) prior to the NDA submission for FDA review and comment. These documents may be submitted to your pre-IND file.

Question 3: *As described in our CMC section of this meeting package, Luitpold will (b) (4) Does the Agency accept this approach?*

FDA Response to Question 3:
No, we do not agree. (b) (4)
(b) (4)

(b) (4)

Please note that the final determination for user fees occurs when the applications are submitted in their entirety to the FDA.

Question 4: *Luitpold has provided both pre-approval and post-approval stability specifications and protocols in the meeting package (refer to section 2.3.P.8). Luitpold proposes to utilize these for the forthcoming registration batches (pre-approval protocol) and for future commercial batches upon NDA approval (post-approval protocol). Does the Division concur?*

FDA Response to Question 4:
The proposed stability protocols appear to be acceptable.

Question 5: *Drug product specifications for release are provided in section 2.3.P.5 of this meeting package. Does the Division concur with the proposed specifications?*

FDA Response to Question 5:
Overall, your drug products specifications appear to be acceptable. However, we are concerned about the proposed acceptance criteria for pH, i.e. 1.5 – 3.5 for (b) (4) (Trace Elements Injection, USP) that may not be suitable for an injectable dosage form. You also need to specify acceptance criteria for (b) (4) impurities listed as "TBD" throughout the proposed specifications for drug products. Acceptance criteria for each of the impurities should be established on the basis of Permitted Daily Exposure (PDE), taking into consideration the maximum daily dose that is recommended for your product. Please refer to ICH Guideline for Elemental Impurities, Q3D, version 4, dated 16 December 2014 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf)

Meeting Discussion:
Luitpold proposes to address and justify the proposed pH range issue in the pre-NDA meeting package. The sponsor will justify the (b) (4) impurities limits for the (b) (4) finished product in the pre-NDA meeting package as well.

3.0 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.

4.0 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

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review.

Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

6.0 505(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, in part, 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, in part, 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, in part, 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.

7.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

8.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

MATTHEW B BRANCAZIO
09/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 123432

MEETING MINUTES

Luitpold Pharmaceuticals, Inc
Attention: Marsha E. Simon
Senior Manager, Regulatory Affairs
800 Adams Avenue
Norristown, PA 19403

Dear Ms. Simon:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Multitrace (trace elements injection).

We also refer to the telecon between representatives of your firm and the FDA on November 12, 2014. The purpose of the meeting was to discuss the possible filing of one or more 505(b)(2) New Drug Application(s) (b) (4)

A copy of the official minutes of the telecon 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, Regulatory Project Manager at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

CDR Matthew Brancazio, Pharm.D.
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: Pre-IND

Meeting Date and Time: November 12, 2014 from 1:00 – 2:00 pm EST
Meeting Location: Teleconference

Application Number: PIND 123432
Product Name: Multitrace (trace elements injection)
Indication: **Total Parenteral Nutrition**
Sponsor/Applicant Name: Luitpold Pharmaceuticals, Inc

Meeting Chair: Ruyi He
Meeting Recorder: Matthew Brancazio

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Joyce Korvick, M.D., Deputy Director of Safety, Division of Gastroenterology and Inborn Errors Products
Ruyi He, M.D., Medical Officer Team Leader, Division of Gastroenterology and Inborn Errors Products
Karyn Berry, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products
Marie Kowblansky, Ph.D., CMC Lead, Office of New Drug Quality Assessment
Sushanta Chakder, Ph.D., Nonclinical Team Leader, Division of Gastroenterology and Inborn Errors Products
Dinesh Gautam, Ph.D., Nonclinical reviewer, Division of Gastroenterology and Inborn Errors Products
Christina Capacci-Daniel, Ph.D., Consumer Safety Officer, Office of Compliance
Peter Chen, RPh, PDUFA Staff, Office of Management
Christina Kirby, Pharm.D., PDUFA Staff, Office of Management
Robert Kosko, Pharm.D., MPH, Senior Regulatory Project Manager, Drug Shortage Staff
Kathy Jaya, M.S.N., J.D., Regulatory Counsel, Office of Unapproved Drugs and Labeling Compliance
James Carr, MPAS, PA-C, Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Matthew Brancazio, Pharm.D., Senior Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products

SPONSOR ATTENDEES
Marc Tokars, Vice President, Clinical Operations
Sylvan Hurewitz, MD, Medical Director, Clinical Development
Andy He, Manager, Medical Affairs
Ken Thompson, DVM, Head of Preclinical Development
Marsha E. Simon, Senior Manager, Clinical Regulatory Affairs
Richard Lawrence, Director of Research and Development
Felicia Bullock, Sr. Director of Regulatory Affairs
Gopal Anyarambhatla, Vice President of Research and Development

1.0 BACKGROUND

The purpose of this meeting is to discuss the possible filing of one or more 505(b)(2) New Drug Application(s) (b) (4) This product is currently a marketed, unapproved drug for use within the United States. This is the first meeting between Luitpold Pharmaceuticals, Inc. and the Division of Gastroenterology and Inborn Errors Products under PIND 123432.

2.0 DISCUSSION

2.1. Clinical

Question 1: *Luitpold believes the data in the literature supports the safety and efficacy of our current commercial Multitrace® (Trace Elements Injection) products for use in total parental nutrition (TPN) and hence approval via a 505(b)(2) application is appropriate? Does the Division agree?*

FDA Response to Question 1:
Yes, we agree that the 505(b)(2) regulatory pathway is appropriate if you intend to rely on published literature to support the Multitrace application.

Literature may be used to support safety and efficacy of your products. We will require published literature to support each component and dose that you intend to include in each of your products. Should your proposed concentration/dose deviate from the literature, you will need to provide adequate justification.

Also, see Section 6.0 for additional information regarding the submission of a 505(b)(2) application.

Meeting discussion:
The sponsor asked if the FDA agrees with the following:
As presented in the literature in our meeting package, for some of the individual trace elements, efficacy is demonstrated at doses much higher than in the current formulations (commercial product) or ASPEN guidelines. These higher doses were initially given to correct deficiencies or to increase serum/plasma levels and then may

have been reduced for maintenance purposes. As individual elements are available to treat deficiencies as the need occurs in individual patients, (b) (4)

If the product is intended for maintenance dosing, the literature submitted to support the NDA will need to address the appropriate maintenance dose, not the dose for addressing deficiencies. If your dose differs from literature for maintenance dosing, you will need to provide adequate scientific rationale for the difference.

The sponsor asked if the FDA agrees with the following:
Clarification is needed regarding the comment cited on page 2 and 5. As the Division is aware, the safety and efficacy data included in our meeting package is predominantly adult case reports. Prior to submitting our 505(b)(2) NDA, Luitpold plans to perform another literature search to ensure there is no new information available. If no further data is available in the literature, would a 505(b)(2) NDA composed primarily of case reports be acceptable?

Luitpold will need to supply scientific rationale based on the literature to justify the dose. Case reports alone will not be sufficient.

The sponsor asked if the FDA agrees with the following:
(b) (4)

Adult literature will not be adequate to support pediatric labeling. Additionally, you will need to provide adequate scientific justification based on your review of the pediatric literature to justify pediatric doses.

Question 2: *Luitpold believes the published nonclinical literature defines the safety and toxicity of Multitrace® (Trace Elements Injection) for the single elements when given intravenously in animals in ascending doses. No information was found where all the trace elements were used in combination. In humans, very small amounts of these trace elements are given intravenously as a parental nutrition supplement. Due to these trace elements being given at very low dosage levels, it is considered that toxicity is unlikely to occur. Therefore, no further nonclinical work will be undertaken by Luitpold. Does the Division agree?*

FDA Response to Question 2:
Yes, we agree.

Question 3: (b) (4)
(b) (4)

(b) (4)

FDA Response to Question 3:

The *Guidance for Industry – Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* provides that original combination products with differing active ingredients should be submitted in separate original applications. Products with like combinations of active ingredients, but with excipients that differ qualitatively or quantitatively with respect to colors, flavorings, adjustment of pH or osmolality, or preservatives, should be submitted in a single original application unless the differences in inactive ingredients would require separate clinical studies of safety or effectiveness, in which case it should be submitted in separate applications. (b) (4)

***Guidance for Industry – Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*:**
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf

Question 4: *Does the Division concur that a matrixing approach, performed in accordance with ICH Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products, would be acceptable to allow for reduced stability testing of the three primary exhibit batches of each formulation?*

FDA Response to Question 4:

Yes, a bracketing and matrixing approach will be allowed, but we suggest that prior to NDA submission, you submit your product-specific matrixing plan for review.

Meeting discussion:

The sponsor asked if the FDA agrees with the following:
Luitpold will submit our product specific matrix plan towards our pre-IND (123432). Is this plan acceptable?

Yes, this is acceptable.

Question 5: *No DMFs are available for the Active Pharmaceutical Ingredients (APIs) used in the drug product formulation* (b) (4) *As such, Luitpold has identified suppliers of these materials that conform with their USP compendial monographs and USP residual solvent contents.* (b) (4) *limited information regarding the manufacturing process, synthesis, structural elucidation, and API stability data is available for inclusion in our NDA submissions. Does the Division concur that the use of these materials is acceptable?*

FDA Response to Question 5:
No, we do not agree. For all drug substances, (b) (4) FDA requires that a description of the manufacturing and characterization procedures be included in the NDA.

Per Section 505(d)(3) of the Food, Drug and Cosmetic Act, no drug application can be approved if the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity. The *guidance* "FDA Guidance *for industry*: *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*" provided minimum expectations for current good manufacturing practices (CGMPs) used to assure that a drug meets the quality requirements as described in the Act.

During the review process, an assessment will be made of the CGMP compliance of all manufacturing facilities. As such, all facilities need to be identified in the application and must be ready for FDA inspection at the time the drug application is submitted.

Sufficient manufacturing process, synthesis, characterization, and stability information for the active pharmaceutical ingredients (APIs) must be provided in the drug application so that a thorough review can be completed. Chiefly, there must be sufficient data to ensure that the described methods, controls, and facilities will produce drug substance and drug product with the identity, strength, quality, purity, and stability purported in the application.

For specific information regarding the manufacture of API's according to 21 CFR 210 & 211, please refer to the guidance "FDA Guidance for Industry: *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*." The link is provided below:

1) FDA Guidance for Industry – Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf

Meeting discussion:
The sponsor asked if the FDA agrees with the following:

As DMFs are unavailable for these active drug substances, would it be acceptable to the Agency for Luitpold to provide the available (complete) information from the vendor in the form of CMC documentation for each substance within the NDA, including a full description of the manufacturing process, synthesis, characterization procedures, and generate API stability data for API concurrent with finished product internally?

Yes, this is acceptable.

Question 6: *Given the aforementioned limitations in material supply for pharmaceutical use, it will likely be difficult to obtain multiple lots of each API for the manufacture of registration batches.* (b) (4) *Does the Division concur that one lot of each API can be utilized for all NDA registration lots?*

FDA Response to Question 6:
It will be acceptable for you to use a single lot of drug substance for all NDA registration lots. However, with regard to your comment about impurity profiles, while we agree that organic impurities are not of great concern, there is a greater probability of ionic elemental impurities being incorporated into these types of drug substances. Consequently, we will require testing for elemental impurities in the finished drug product specification (see response #9).

Question 7: *Luitpold intends to provide a minimum of three lots of stability data for legacy drug product lots for each drug product formulation as supplemental data for NDA submission purposes. This information will consist of data for accelerated (40°C) studies and long-term storage (25°C). Does the Division concur with Luitpold's proposal to include six months of data (stored at 40°C/75% R.H., 30°C/65% R.H., and 25°C/60% R.H.) for the registration lots at the time of NDA submission?*

FDA Response to Question 7:
Yes, we agree.

Question 8: *Luitpold has provided both pre-approval and post-approval stability protocols in the meeting package (refer to sections 2.3.P.8 and 3.2.P.8). Luitpold proposes to utilize these for the forthcoming registration batches (pre-approval protocol) and for future commercial batches upon NDA approval (post-approval protocol). Does the Division concur?*

FDA Response to Question 8:
Yes, we agree with your proposed stability protocols as presented in the referenced sections of your submission.

Question 9: *Drug product specifications for release and stability are provided in sections 3.2.P.5.1 and 3.2.P.8.1, respectively, of this meeting package. For ease of review, a*

summary of the drug product specifications and their associated justifications are provided in the following table. Does the Division concur with the proposed specifications?

FDA Response to Question 9:
Your proposed drug product specifications are reasonable. However, we request that you add testing for (b) (4) and any other (b) (4) that have the potential to contaminate your product during manufacture. Acceptance criteria for each of the impurities should be established on the basis of Permitted Daily Exposure (PDE), taking into consideration the maximum daily dose that is recommended for your product. While not yet finalized, PDEs recommended by ICH for parenteral products represent the best thinking on this subject at the present time.

Question 10: (b) (4)

Does the Division agree?

FDA Response to Question 10:
See response to Questions 1 and 3.

3.0 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.

4.0 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

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

6.0 505(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, in part, 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, in part, 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, in part, 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.

7.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

8.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

MATTHEW B BRANCAZIO
11/13/2014