# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209575Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 106499

**MEETING MINUTES**

Lannett Holdings, Inc.
13200 Townsend Road
Philadelphia, PA 19154

Attention: Katy Rudnick
Manager, Regulatory Affairs

Dear Ms. Rudnick:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution.

We also refer to the meeting between representatives of your firm and the FDA on April 18, 2017. The purpose of the meeting was to discuss the plan for a 505(b)(2) NDA submission for Cocaine hydrochloride topical solution.

A copy of the official minutes of the meeting 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) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Diana L. Walker, PhD
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes


Reference ID: 4563674

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

# MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** April 18, 2017, 4:00 p.m. - 5:00 p.m. (Eastern)
**Meeting Location:** Teleconference

**Application Number:** IND 106499
**Product Name:** Cocaine Hydrochloride Topical Solution, 4% and 10%
**Indication:** Introduction of local (topical) anesthesia of accessible mucous membranes of the nasal cavities
**Sponsor Name:** Lannett Holdings, Inc.

**Meeting Chair:** Rigoberto Roca, MD, Deputy Director, DAAAP
**Meeting Recorder:** Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

| Industry Representatives | Title |
|---|---|
| Kristie Stephens | Vice President, Regulatory Affairs & Chief Compliance Officer |
| Katy Rudnick | Manager, Regulatory Affairs |
| Ashley McKenzie | Senior Associate, Regulatory Affairs |
| (b) (4) | Consultant to the CEO |
| Adriana Arismendi | Director of Corporate Excellence, R&D Project Management |
| Michelle Renfors | Vice President, Product Development, Cody Laboratories, Inc. |
| Steve Hartman | Vice President, Compliance Cody Laboratories, Inc. |
| Howard Melcher | Manager, Regulatory Affairs, Cody Laboratories |

(b) (4)

| FDA | Title |
|---|---|
| Rigoberto Roca, MD | Deputy Director, DAAAP |
| Leah Crisafi, MD | Clinical Team Leader, DAAAP |
| Renee Petit-Scott, MD | Medical Officer, DAAAP |
| Daniel Mellon, PhD | Pharmacology-Toxicology Supervisor |
| Newton Woo, PhD | Pharmacology-Toxicology Team Leader |
| Belinda Hayes, PhD | Pharmacology-Toxicology Reviewer |
| David Petullo, PhD | Biometrics Team Leader |
| Feng Li, PhD | Biometrics Reviewer |

| | |
|---|---|
| Julia Pinto, PhD | Branch Chief, Branch IV, Division of New Drug Products II (DNDPII), Office of New Drug Products (ONDP), Office of Product Quality (OPQ) |
| Ciby Abraham, PhD | Acting Pharmaceutical Assessment Lead, ONDP/OPQ |
| Yun Xu, PhD | Clinical Pharmacology Team Leader |
| Deep Kwatra, PhD | Clinical Pharmacology Reviewer |
| Katherine Bonson, PhD | Controlled Substances Staff |
| Deborah Myers, RPh, MBA | Safety Evaluator, DMEPA |
| Diana Walker, PhD | Sr. Regulatory Project Manager, DAAAP |

## 1.0 BACKGROUND

(i) The purpose of this meeting is to discuss and gain agreement with the Agency on the contents of a 505(b)(2) NDA for Cocaine Hydrochloride Topical Solution, 4% and 10%, to ensure that it will be accepted for filing.

(ii) Cocaine Hydrochloride Topical Solution is currently a marketed, unapproved drug.

(iii) Lannett intends to file a 505(b)(2) NDA for this product under the sponsor Cody Laboratories, Inc., a wholly owned subsidiary of Lannett Company, Inc. The 505(b)(2) will reference published literature.

(iv) The Applicant plans to seek the indication "for the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through accessible mucous membranes of the nasal cavities."

(v) The Agency sent preliminary responses to the Sponsor via email on April 13, 2017.

(vi) The Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

## 2. DISCUSSION

*Question 1. A proprietary name is planned for this drug product. We plan to submit the request for proprietary name review to the IND prior to NDA submission. If the proprietary name is found to be conditionally acceptable under the IND application, the name will also be submitted for review in the NDA. Does the Agency agree to this plan?*

*Alternatively, if the proprietary name is not found to be conditionally acceptable, the sponsor proposes to provide an alternate proprietary name for review as soon as it becomes available which may not be within the original NDA submission. Does the Agency have any concerns with this?*

**FDA Response:**
**Yes, we agree with your plan to submit your request for a proprietary name review during the IND phase of your drug development. The content requirements for such a submission can be found in the draft guidance for industry: *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.**

**Additionally, we agree that if your proposed proprietary name is found to be conditionally acceptable during the IND phase then a request for proprietary name review, for the proprietary name previously found conditionally acceptable, should also be submitted for review in your NDA submission.**

**Alternatively, we agree that if the proposed proprietary name is not found to be conditionally acceptable, you can then provide an alternate proprietary name for review. In order to initiate the review of the alternate proprietary name, you would need to submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.**

**If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following draft guidance for industry: *Best Practices in Developing Proprietary Names for Drugs*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf.**

Discussion:
There was no further discussion of this question.

*Question 2. The sponsor plans to utilize the generic drug name (Cocaine Hydrochloride Topical Solution, 4% and 10%) throughout the NDA submission. Only the proposed labeling and promotional documents will include the proposed proprietary nomenclature. Does the Agency agree this is acceptable?*

**FDA Response:**
**We agree with your plan to utilize the generic name to reference your drug product throughout the NDA submission and include the proprietary name in the proposed labeling and promotional documents.**

Discussion:
There was no further discussion of this question.

*Question 3. The sponsor plans to submit a very brief scheduling request for the Cocaine*

*Hydrochloride Topical Solution, 4% and 10% as a CII controlled substance. Congress scheduled cocaine as DEA Schedule II when the Controlled Substances Act was passed, and Lannett is not proposing a change from the current DEA Schedule II. Lannett did not observe any evidence of diversion, addiction, or abuse in any of its clinical trials. There were no irregularities in drug accountability, and no theft or diversion was reported during any of the clinical trials. Does the Agency agree with the proposed scheduling of this drug product?*

**FDA Response:**
**Yes, we agree.**

Discussion:
There was no further discussion of this question.

*Question 4. The sponsor believes that this product does not require an environmental assessment and plans to request a waiver based on qualification for a categorical exclusion under 21 CFR § 25.31(b). Although the action of filing an NDA (and subsequent NDA approval) may increase the use of the active moiety, the estimated concentration of cocaine hydrochloride at the point of entry into the aquatic environment will be well below 1 part per billion (ppb) (21 CFR 25.31(b)). The following calculation was used to determine the estimated introduction concentration (EIC) of cocaine hydrochloride. The calculation is based on a five-fold increase of estimated commercial production levels (b) (4) kg/year) of cocaine hydrochloride.*

$$EIC\ Aquatic = \frac{(b)\ (4)\ kg\ Cocaine\ HCl}{year} * \frac{day}{(b)\ (4)\ liters^{1}} * \frac{year}{65\ days} * \frac{(b)\ (4)}{kg} = (b)\ (4)\ ppb$$

[1]Source: 1996 Needs Survey, Report to Congress

*Does the Agency agree that an environmental assessment waiver will be approved based on this categorical exclusion?*

**FDA Response:**
**While your rationale to request a waiver for categorical exclusion appears to be acceptable, provide justification with calculations in your NDA. Whether the environmental assessment is adequate will be determined during the NDA review.**

Discussion:
There was no further discussion of this question.

*Question 5. The sponsor will perform a search of the published scientific literature for reports relevant to the clinical safety and effectiveness of cocaine hydrochloride using an*

*appropriate cut-off date. Published literature will be cited for supportive information throughout the NDA in all appropriate documents. Where published literature is cited, we will hyperlink from the document it is referenced in to the PDF copy of the article and/or data in Modules 2.7.5, 3.3, 4.3, and 5.4 or as appropriate. Does the Agency agree with this approach?*

**FDA Response:**
**We agree with your plan to perform a search of the published scientific literature for reports relevant to clinical safety and effectiveness of cocaine hydrochloride. We request, however, that the "appropriate cut-off date" be further clarified. Your safety database should include a comprehensive review and analysis of the worldwide published literature to identify safety concerns regarding the use of cocaine hydrochloride topical solution. Including studies or case narratives from the published literature involving the misuse and abuse of cocaine may further inform any safety concerns not captured in the review and analysis of sources citing its therapeutic use. We agree with your plan to include the published literature references in the appropriate Modules of your NDA submission. Note that all articles need to be translated into English.**

Discussion:
The Sponsor clarified that the literature search cut-off date will be April 30, 2017, and that they have included articles dating back to the 1970s. Information from their published literature search to be included in the NDA submission will contain the following:

- Search engines and criteria utilized to conduct the literature search(es)
- All relied-upon articles (full length)
- Article summaries provided in the appropriate sections of Module 2
- Pertinent information, clinical and nonclinical, from the published literature integrated into the appropriate modules and sections throughout the NDA submission

The Agency agreed that the proposed published literature search dates and the proposed plan for incorporating the findings from the literature search into the NDA submission are acceptable.

*Question 6. The Sponsor believes that all non-clinical and toxicology commitments have been met. The studies include:*

- *Phase I PK plasma, urine and vasoconstriction study in humans (4% and 10% strengths), Protocol Number: LNT-P6-733 Version 4.2 (Attachment 19), titled "Single Dose Crossover Bioavailability Study of Cocaine HCl 4% and 10% Solutions Following Topical Application in the Nasal Cavity in Healthy Male and Female Volunteers". The synopsis from the final Clinical Study Report LNT-P6-733 is provided (Attachment 20).*

- *14-Day Repeat Dose Intranasal Instillation Toxicity Study in Sprague-Dawley Rats of finished product 4% w/v and 10% w/v spiked with impurities to their*

*maximum stability levels, Protocol Number: P16-0633-00B (Attachment 21). The study summary, 16-01711-G1, is also provided (Attachment 22).*

- *Ames test for all significant impurities* (b) (4) *. The synopses for each study are provided:*
  - (b) (4) *(Attachment 23)*
  - (b) (4) *(Attachment 24)*
  - (b) (4) *(Attachment 25)*

- *Chromosomal aberration test for all significant impurities* (b) (4) *. The synopses for each study are provided:*
  - (b) (4) *(Attachment 26)*
  - (b) (4) *(Attachment 27)*
  - (b) (4) *(Attachment 28)*
    - *In response to a positive result for chromosomal aberration in the* (b) (4) *study we are currently conducting two additional genotoxicity tests for* (b) (4) *in vivo mammalian (rat) alkaline comet assay in liver cells and blood (OECD 489) and in vivo mammalian (mouse) erythrocyte micronucleus (OECD 474) tests will be conducted within a consolidated study.*

- *Salmonella typhimurium and Escherichia coli Reverse Mutation Assay (Ames test) for Cocaine Hydrochloride, USP, Report Number: 11-4138-G1 (Attachment 29)*

- *Chromosomal Aberration Assay for Cocaine Hydrochloride, USP, Report Number: 11-4138-G2 (Attachment 30)*

- *Rodent Bone Marrow Micronucleus Assay for Cocaine Hydrochloride, USP, Report Number: 11-4138-G3 (Attachment 31)*

- *QSAR and Leadscope Model Applier Assessments to Meet the Requirement of ICH M7 (Step 4) for Cocaine related impurities, Date: March 16, 2015 (Attachment 32)*

- *A toxicology literature evaluation of benzoate (drug product* (b) (4) *) (Attachment 33)*

- *Reviews of published literature were conducted, and the documents have been previously submitted to the IND.*

  *Does the Agency have any comments?*

**FDA Response:**
**Based on your meeting package, the appropriate nonclinical studies were conducted to address the genotoxic potential of cocaine and the genotoxic and general toxicity potential of the drug substance impurities that exceeded ICH qualification thresholds. Your proposal to conduct an in vivo micronucleus and comet assay for (b) (4) in response to the positive result in the chromosomal aberration study is acceptable.**

**As discussed in previous meetings, your 14-day repeat-dose intranasal toxicity study should have been designed to qualify several novel excipients (for the intranasal route of administration): sodium benzoate, D & C Yellow #10, and FD & C Green #3 novel excipients. However, in the summary report submitted in the pre-NDA meeting package, it is not clear whether D & C Yellow #10 and FD & C Green #3 were evaluated in this study. Clarify whether the to-be-marketed cocaine (4% and 10%) solutions were used in the study to confirm that the study also tested these novel excipients.**

**On the surface, the submitted nonclinical summaries in the meeting package do not appear to reflect a comprehensive literature review. We remind you that you must conduct a comprehensive review of the literature and specifically address what studies provide the most relevant data with respect to current ICH requirements. Submit the search strategies you employed and provide justification that you have completed a comprehensive literature review in the NDA.**

Discussion:
The Sponsor clarified that the 14-day repeat-dose intranasal toxicity study did qualify the excipients sodium benzoate, D & C Yellow #10, and FD & C Green #3. The study followed the agreed-upon study design and did use the to-be-marketed cocaine (4% and 10%) solutions, vehicle, and sterile water. The Sponsor informed the Agency that the study results were all negative.

The Sponsor confirmed that a full literature search will be provided, as described in the discussion under Question #5.

*Question 7.* *The Sponsor believes that the biopharmaceutics and clinical pharmacology package consisting of a Phase I Pharmacokinetic study "Single Dose Crossover Bioavailability Study of Cocaine HCl 4% and 10% Solutions Following Topical Application In The Nasal Cavity In Healthy Male And Female Volunteers" (Protocol: LNT-P6-733, Attachment 19) conducted using the application methods and maximum dosage available in the Phase III clinical trials along with available published literature (previously submitted to the IND) is adequate to support the NDA for use in the adult patient population. Does the Agency agree?*

**FDA Response:**
**We cannot agree at this stage, as adequacy of the data and the literature for the NDA will be determined during review of the NDA. A complete clinical pharmacology package is expected at the time of NDA submission. Hence, you must address all pertinent clinical**

**pharmacology information related to the following aspects of the drug and the pharmacokinetics of the drug in special populations including but not limited to: (1) absorption, (2) distribution (e.g., in vivo study with radiolabeled product), (3) metabolism (e.g., in vitro study using human microsomes/hepatocytes and/or analyze plasma samples from in vivo studies from assessment of potential metabolites), (4) elimination (e.g., collect urine and feces samples in phase 1 studies to determine elimination pathways), (5) PK and dosing in special populations (e.g., effect of age, gender, hepatic and renal impairment), (6) drug interaction potential (e.g., in vitro enzyme and transporter induction and inhibition properties of your drug and in vivo studies if warranted), and (7) QT prolongation potential. This information can be obtained from dedicated studies or sub-population analyses in Phase 3 studies) or from the public domain (if information of adequate quality is available in the published literature).**

**If literature articles are used as the source of this information, full articles must be included in the NDA. These PK studies must be of adequate sample size, and include validated analytical assays for cocaine and its metabolites.**

**For all human PK studies you cite or summarize from literature, provide the bioanalytical validation/performance data and raw PK data in your NDA submission. We recommend you contact the authors to obtain such information and submit it as a part of your package. Due diligence is required to acquire such information about the studies, otherwise you must provide adequate justification that the required information is not obtainable and why the results from the literature can still be used to support your proposed product.**

**You must provide adequate information or data to address the PK changes of your product in specific population such as patients with renal or hepatic impairment, and drug-drug interaction. Since your product is a local acting product, the main consideration will be whether systemic drug exposure will increase in such situations and lead to concerns of systemic safety. Note your product is local acting product, so dose reduction may not be a viable option since it will affect local efficacy of your product. Provide data or dose recommendation to address nasal conditions that may affect absorption of your product such as rhinitis, or use of a nasal decongestant.**

**Use your final to-be-marketed formulation in the PK studies and clinical safety and efficacy studies. Otherwise, you will need to provide adequate bridging information or justification why the study results can apply to your final to-be-marketed product.**

Discussion:
There was no further discussion of this question.

*Question 8.* *The clinical efficacy program is comprised of two Phase III studies, COCA-4vs10-001 and COCA4vs10-002.* (b) (4) *the 002 study showed statistical significance for efficacy for both the Cocaine HCl 4% and 10% solutions. The sponsor confirms that the two studies conducted in accordance*

*with the SPA agreements dated December 16, 2011, September 24, 2013, July 9, 2015, and March 21, 2016 (Attachments 3, 5, 12 and 14) demonstrate that they provide sufficient evidence of efficacy for the proposed indication. Summary data for both studies are provided in the pNDA meeting package as noted below.*

*The data tables and synopsis for COCA4vs10-001 (Attachment 34)*
*The data tables and synopsis for COCA4vs10-002 (Attachment 35)*

*Does the Agency agree?*

**FDA Response:**
**A thorough review of the results from your Phase 3 studies has not been conducted. It appears that your Phase 3 study COCA4vs10-002 was completed in accordance with the SPA agreement, whereas study COCA4vs10-001 was not due to lack of efficacy of the 4% topical solution. Our determination of safety and efficacy will be based upon the totality of the data.**

Discussion:
There was no further discussion of this question.

*Question 9.* *We will provide the statistical analysis plans (SAP) in the pNDA meeting package for the Phase I and Phase III clinical studies that contain the analyses, tables, listings, and figures. These tables contain the data to be used in the Clinical Study Reports. Please refer to Numbers 4 and 5 below for document hyperlinking. Does the FDA have any further comments?*

**FDA Response:**
**The adequacy of the analyses, tables, listings, and figures in your study report will be determined during the NDA review cycle. Additional analyses, tables, and figures may be requested if deemed necessary.**

Discussion:
There was no further discussion of this question.

*Question 10.* *After further review, the Sponsor intends to summarize the efficacy in the ISE analysis from the two Phase III studies and the one Phase I study in combination. All three of the studies will be integrated and a pooled analysis and a meta-analysis will be presented. The ISE plan is provided in the pNDA meeting package (Attachment 36). Does the Agency agree with the proposed analysis plan for the efficacy data?*

**FDA Response:**
**In general, the ISE should be more than just a pooled analysis of your clinical studies. It should be a comprehensive discussion about the effectiveness of your drug product,**

**including information from your clinical and nonclinical studies and the published literature.**

**With respect to your Phase 3 studies, the randomization ratios differed. Study COCA4vs10-001 used a randomization ratio of 1:1:1 and Study COCA4vs10-002 used a randomization ratio of 2:2:1. Therefore, simple or naïve pooling is not appropriate. Your proposal, however, to perform a weighted meta-analysis appears acceptable.**

Discussion:
There was no further discussion of this question.

*Question 11. For the NDA, the sponsor intends to summarize the safety in the ISS analysis from the two phase III studies and the one Phase I study in combination. All three of the studies will be integrated with pooling of data. The ISS plan is provided in the pNDA meeting package (Attachment 37). Does the Agency agree with the proposed analysis plan for the safety data?*

**FDA Response:**
**We concur that the evaluation of adverse events (AEs) for all treatment groups in the integrated data pool is appropriate as long as the integrated data pool includes all studies conducted. Additional safety analyses should include summaries of specific targeted AEs including those related to cocaine toxicity, extent of exposure, changes in vital signs, and changes in nasal mucosa and smell. The ISS must conform with the requirements of 21 CFR 314.50(d)(5)(vi)(a), to include analyses by dose and surgical procedure performed, as well as by patient subgroups. Differences found between the studied and the to-be-marketed formulations need to be addressed as well.**

Discussion:
The Sponsor stated that they plan to include procedure, dosage, age, and gender subgroups and asked whether this is acceptable. The Agency stated that the Sponsor must adhere to the requirements of 21 CFR 314.50(d)(5)(vi)(a), which includes other subgroups such as race. The Sponsor agreed to provide all safety data for the required subgroups.

*Question 12. The Sponsor has reached an agreement for its iPSP with the Agency, a copy of the Agreed Initial Pediatric Study Plan – Agreement (Attachment 16) is provided herein. Lannett has already initiated action items according to the approved plan including commencement of literature searches and surveying physicians on pediatric use. Lannett will update the FDA as more information becomes available. Does the FDA have any further comments?*

**FDA Response:**
**Your plan to provide updated information as it becomes available is acceptable. We currently have no further comment regarding your pediatric development plan.**

Discussion:
The Sponsor provided an update on the pediatric literature search and their survey of practitioners regarding the actual use of topical cocaine in the pediatric population. The results of their literature search revealed a lack of evidence [redacted] and thus they are in the process of preparing a protocol for this study. The Sponsor stated that these presubmission activities are taking longer than anticipated, and asked whether the delay may lead to an NDA filing issue or would require amendments to either the PSP or the NDA once submitted. The Division clarified that the Sponsor's failure to adhere to the milestone dates in their agreed initial PSP would not constitute a filing issue. The Division recommended that the Sponsor submit rationale, including a summary of current efforts and progress, to support revised milestone dates when the NDA is submitted. The Division will review the information and finalize the PREA requirement during the review cycle.

*Question 13. The Sponsor has designated [redacted] as the API Starting Material for the manufacture of the drug substance, cocaine hydrochloride. A Type C meeting was held on December 15, 2016; the meeting minutes are provided (Attachment 18). Does the Agency have any further comments?*

**FDA Response:**
**No, we do not have any further comment at this time on the regulatory starting material for the drug substance. We still recommend that [redacted] be established as the regulatory starting material unless the concerns as outlined in the December 15, 2016, Meeting Minutes are addressed adequately.**

Discussion:
There was no further discussion of this question.

*Question 14. In addition to passing drug product stability data, what additional data or supporting information would be required in order to support a [redacted] that has not met USP UV absorbance testing specifications?*

**FDA Response:**
**Provide the following information:**

- **Detailed testing data for th [redacted]**
- **Supporting photostability and stress data to demonstrate that the product remains stable in this container closure system using the [redacted].**
- **Extractable and leachable data per <1663> and <1664> that demonstrates a good correlation between extractables and leachables.**

Discussion:
The Agency asked the Sponsor for clarification as to whether the statement "to support a (b) (4) that has not met USP UV absorbance testing specifications" was in reference to the ability of the closure to protect from UV light or in regard to extractables. The Sponsor stated that it was neither, and that they have no evidence of problems regarding either light protection or extractables. The Sponsor further explained that the failure was in testing the (b) (4) material used to make the (b) (4) The Sponsor stated that they plan to submit a full package of data as requested in the comments from the Agency.

Question 15. *FDA stated in the pIND correspondence (Attachment 1) that we need to submit stability data to support the diluted solution (Q3). We do not recommend dilution of the product prior to use and intend to include this statement in the labeling, and therefore, do not plan to submit stability data to support the diluted solution. Does the Agency agree*?

**FDA Response:**
**We agree that stability data of the diluted product is not required if the drug product will not be diluted in any way prior to administration.**

Discussion:
There was no further discussion of this question.

*Question 16. A leachables and extractables evaluation of the container and closure systems will be provided in Module 3.2.P.7. We are also conducting an extractables study for the (b) (4). The report will be provided in Module 3.2.P.3.3. Does the Agency have any comments?*

**FDA Response:**
**Your proposal to include leachables and extractables data in Module 3.2.P.7 is acceptable and we have the following comments:**

**Adequate information on potential leachables and extractables from the drug container closure system and/or drug product formulation must be included in your NDA submission. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Provide justification for the choice of solvents and conditions for the extraction studies (time, temperature, etc.). The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) must be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you must provide adequate justification that these thresholds are not possible to be met by current analytical**

**methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission must include a detailed discussion of how you established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.**

**Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.**

**For all drug products, establish your AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., 120 mcg/day for an acute use product). However, from a general toxicology perspective, the AET must be able to detect and identify any leachable that is present in the product at 5 mcg/day or higher in order, unless justified otherwise, to permit an adequate toxicological risk assessment.**

**For additional guidance on extractables and leachables testing, refer to the following documents:**

- **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**
- **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**
- **FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf**

**The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless**

**otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.**

- **If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.**

- **Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your container closure system.**

- **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.**

Discussion:
There was no further discussion of this question.

*Question 17. As per the clinical trial protocols, the drug was delivered via pledgets. We intend to make a statement that the product be administered with pledgets. Does the Agency agree that language modeled after delivery via pledgets conducted in our clinical trials is appropriate to be included in the drug product labeling? Does the Agency have any comments?*

**FDA Response:**
**We agree that the route of administration upon which your safety and efficacy results are based (i.e., application via pledget) should be the route of administration described in the product label.**

Discussion:
There was no further discussion of this question.

*Question 18. The Sponsor will label this product for use by healthcare professionals only. As such, the sponsor believes that a REMS program is not appropriate and not*

*required for this product and does not plan to include REMS documents in the NDA submission. Does the Agency agree that REMS documents will not be required for this NDA?*

**FDA Response:**
**It does not appear at this time that your NDA would require a REMS program. However, a REMS program may be necessary if FDA becomes aware of new safety information.**

Discussion:
There was no further discussion of this question.

*Question 19. Currently there are no ongoing clinical studies (animal or human). We therefore believe that no additional safety reporting is required beyond that which will be submitted within the original NDA. Does the Agency agree that for the 4 month/120-day "safety update report" required by 314.50(d)(5)(vi)(b) a statement of no new information is acceptable? Does the Agency have any comments?*

**FDA Response:**
**The required 4-month/120-day safety update, as outlined in 21 CFR 314.50(d)(5)(vi)(b), should include any new information, foreign or domestic, including pertinent studies or case reports in the published literature and a review of the FAERS cases, and is required to be submitted in the same format as the integrated summary of safety.**

Discussion:
There was no further discussion of this question.

*Question 20. Lannett has a patent for the synthesis of Cocaine HCl API, and intends to list this patent with its NDA. Lannett may also submit additional patent information to the NDA during the review cycle. Does the Agency have any comments?*

**FDA Response:**
**You must submit any required patent certification(s) and any company drug product patents held at the time of submission of your 505(b)(2) application. However, if a patent is issued after the application is filed with FDA but before the application is approved, additional company drug product patents may be submitted within 30 days of the issuance of the patent.**

Discussion:
There was no further discussion of this question.

*Question 21. Lannett did not observe any evidence of diversion, addiction, habituation, or abuse in any of its clinical trials. There were no irregularities in drug*

*accountability, and no theft or diversion was reported during any of the clinical trials. This product is scheduled as a CII product and will be controlled as per the regulations for this scheduling category. Patient access to this product is controlled as this product will be used only in an office setting and administered by a medical professional for single use (per diagnostic or surgical procedure). Does the Agency have any comments?*

**FDA Response:**
**The data from clinical trials regarding abuse potential and drug accountability discrepancies will be reviewed when these data are submitted to FDA in an NDA. Present the data as described below:**

- **For all Phase 1, 2 and 3 studies, any reported adverse events (AEs) associated with potential abuse or overdose should be documented. Case narratives of each of these AEs should be provided, especially for any patient with serious AEs (SAEs). These should include cases involving lack of compliance or patients who discontinue participation without returning the study medication.**

- **The incidence of abuse-related AEs in comparison to placebo in trials should be reported by study, population, dose, and displayed in tabular format. Tables should be created for abuse-related higher level MedDRA terms, even if there were few patients or subjects who experienced a particular AE.**

- **Possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) in all clinical trials. Additionally, you should look for drug accountability discrepancies (e.g., missing medication, loss of drug, or non-compliance cases in which more investigational drug was used, as compared to expected use). Investigators should obtain more information and explanations from the subjects when there are drug accountability discrepancies.**

Discussion:
There was no further discussion of this question.

## ADDITIONAL COMMENTS

**Additional Clinical Comments**
**We request that you provide the following additional information in your NDA submission:**

- **A summary table to include placebo subjects who were able to complete the diagnostic or surgical procedure without the administration of additional anesthetic or analgesic medications and the procedure performed.**
- **A summary table to include subjects in the cocaine treatment arms who experienced an adverse event and the corresponding vital sign measurements (including systolic**

**and diastolic blood pressure, pulse pressure, and heart rate) during the time of the adverse event and extending until its resolution.**

- **For all subjects, a summary table to include all additional anesthetic or analgesic medications administered during the diagnostic or surgical procedure and the specific procedure performed.**

Discussion:
Regarding the first bullet point, the Sponsor clarified the study protocol for the placebo subjects. Specifically, the Sponsor stated that upon conclusion of the von Frey filament testing and the unblinding to placebo or cocaine treatment, the placebo subjects were observed for any adverse events in the post-anesthesia care unit for a period of 90 minutes post-pledget removal, during which time they underwent 12-lead ECG testing. At the conclusion of the 90-minute recovery period, in the absence of adverse events, these subjects were then administered an appropriate topical anesthetic (most commonly lidocaine with oxymetazoline) and proceeded with their planned diagnostic or surgical procedure. The Sponsor stated that their Phase 3 studies were conducted as per the agreed-upon SPA protocol and asked for clarification from the Division regarding the information they should include in the table of placebo subjects. The Division clarified that if any placebo subjects completed the diagnostic or surgical procedure without an anesthetic administration beyond the placebo solution they should be clearly identified. The Sponsor stated that all placebo subjects received an additional topical anesthetic for the procedure and that all medications would be clearly provided under the concomitant medications listing for each subject. The Sponsor further emphasized that they have collected and will provide all of the same information for the placebo subjects as they did for the cocaine-treated subjects.

**Additional Nonclinical Comments**

1. **For your NDA submission, include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

2. **We remind you that for the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2) and ICH Q3B(R2). In order to provide adequate qualification:**

    a. **You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

    b. **In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14-days duration should be completed.**

3. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

4. **We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, conduct a thorough review and integrated analysis of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.**

5. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained.**

6. **We may to refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity, degradant, excipient, or leachable that exceeds the recommended qualification threshold that is not justified for safety otherwise.**

Discussion:
Regarding Comment 5, the Sponsor requested that the Agency provide clarification on exposure margins. The Agency stated that the Sponsor will need to provide justification for the proposed exposure margins that will be included in all relevant nonclinical sections of labelling, which includes the risk summary statement and animal data sections in Section 8. In general, margins are expressed as the human equivalent dose based on body surface area conversion of an animal dose at which adverse events were observed (or in some cases not observed) over the maximum human recommended dose. During the later stages of the NDA review, the Agency will work with the Sponsor during the labeling negotiations to come to agreement on the language and exposure margins, but recommended that the Sponsor look at recently approved labels in PLLR format as examples when they prepare their NDA submission.

## 3. GENERAL Pre-NDA 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 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP 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.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP 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.

## DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs, and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards

specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

## NARRATIVE SUMMARIES

Narratives summaries of important adverse events (e.g., deaths, events leading to discontinuation, other serious adverse events) should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. Narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation/forms, as this adds little value. A valuable narrative summary is written like a discharge summary with a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary:

- Patient age and sex
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Pertinent test results (e.g., lab data, ECG data, biopsy data)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

## SUBMISSION 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.

## SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

## ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

## 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 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. by 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such

pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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 is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). 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 the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the 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 effectiveness 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 A* |
| *3. Example: NDA YYYYYY "TRADENAME"* | *Previous finding of safety for Carcinogenicity, labeling section B* |
| *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.

**Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

a. Number of subjects screened at each site
b. Number of subjects randomized at each site
c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

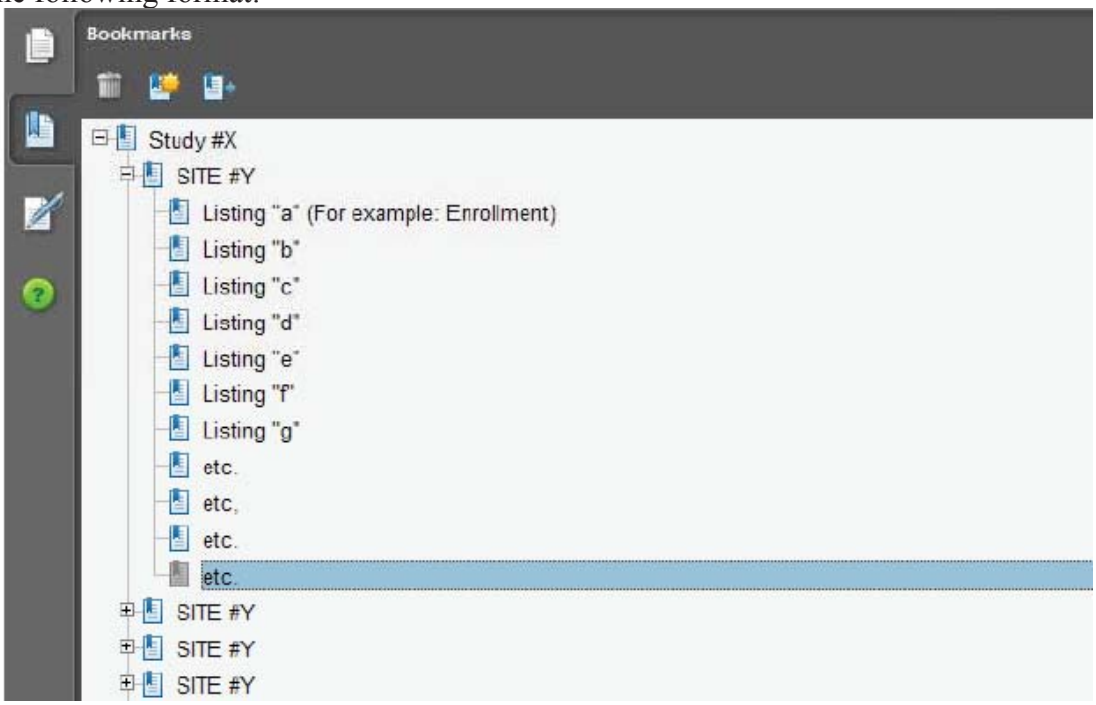
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:




## III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf ) for the structure and format of this data set.

**Attachment 1**
**Technical Instructions:**
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

| DSI Pre-NDA Request Item[1] | STF File Tag | Used For | Allowable File Formats |
|---|---|---|---|
| I | data-listing-dataset | Data listings, by study | .pdf |
| I | annotated-crf | Sample annotated case report form, by study | .pdf |
| II | data-listing-dataset | Data listings, by study (Line listings, by site) | .pdf |
| III | data-listing-dataset | Site-level datasets, across studies | .xpt |
| III | data-listing-data-definition | Define file | .pdf |

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:


C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

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/s/

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DIANA L WALKER
05/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 106499

**MEETING MINUTES**

Lannett Company, Inc.
13200 Townsend Road
Philadelphia, PA 19154

Attention: Kristie Stephens
Director of Regulatory Affairs

Dear Ms. Stephens:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution.

We also refer to the meeting between representatives of your firm and the FDA on January 6, 2015. The purpose of the meeting was to discuss your Cocaine Hydrochloride Topical Solution Phase 3 pivotal study with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

A copy of the official minutes of the meeting 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) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Diana L. Walker, PhD
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

# MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type A
**Meeting Category:** Guidance

**Meeting Date and Time:** January 6, 2015, 3:00 p.m. (Eastern)
**Meeting Location:** 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

**Application Number:** IND 106499
**Product Name:** Cocaine Hydrochloride Topical Solution
**Indication:** Introduction of local (topical) anesthesia of accessible mucous membranes of the nasal cavities
**Sponsor/Applicant Name:** Lannett Holdings, Inc.

**Meeting Chair:** Rigoberto Roca, MD, Deputy Director, DAAAP
**Meeting Recorder:** Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

| **Lannett Representatives** | **Title** |
|---|---|
| Arthur Bedrosian | President and CEO, Lannett Company, Inc. |
| (b) (4) | Consultant to the CEO of Lannett Company, Inc. |
| Partha Basumallik | Director of CRO Services, Lannett Company, Inc. |
| Kristie Stephens | Director of Regulatory Affairs, Lannett Company, Inc. |
| (b) (4) | |
| Michael Bogda | President, Lannett Company, Inc. |
| **FDA** | **Title** |
| Sharon Hertz, MD | Acting Division Director, DAAAP |
| Rigoberto Roca, MD | Deputy Director, DAAAP |
| Amelia Luckett, MD | Medical Officer, DAAAP |
| Thomas Permutt, PhD | Director, Division of Biometrics II (DBII) |
| Yan Zhou, PhD | Biostatistics Reviewer, DBII |
| Diana Walker, PhD | Sr. Regulatory Project Manager, DAAAP |

## 1.0 BACKGROUND

a. Lannett has submitted this Type A meeting request to discuss a proposed amendment to the trial protocol and the Special Protocol Assessment (SPA) agreement with FDA based on the unexpected outcome from an interim clinical trial data review that Lannett has performed.

b. The trial protocol was developed in conjunction with the FDA and in accordance with a written Special Protocol Assessment (SPA) agreement. The clinical trial has been suspended and the proposed revised clinical plan needs to be discussed with the FDA and agreed upon in order for the trial to continue. Lannett proposes changes to the trial protocol and based on the aforementioned data review.

c. The Sponsor received the Agency's preliminary responses to the current meeting questions on December 30, 2014, via email.

d. At the meeting the Sponsor distributed a handout containing points they wanted to make during the meeting. This handout is appended to these meeting minutes.

e. The Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

## 2.0 DISCUSSION

*Question 1. Would the FDA accept continuing this trial with a revised sample size estimation?*

**Agency Response:**
**Since the family-wise type I error has been exhausted for the efficacy analysis using 100% of the efficacy data, you cannot continue the current trial with the revised sample size estimation for further efficacy analyses. We recommend that you finish the current trial with collection of the remaining safety data.**

Discussion
See "General Meeting Discussion" below.

*Question 2. Would the FDA prefer Lannett restart under a new protocol?*

**Agency Response:**
**Based on the submitted interim data review report, the 4% cocaine solution failed to meet the original criteria outlined in the clinical trial protocol for the primary endpoint. In order to demonstrate a statistically significant increase in treatment success of the 4% cocaine arm relative to the placebo, a new study is required. As the current trial has**

(b) (4) **based on your report, the new study could include two treatment arms, 4% cocaine arm and placebo arm.**

Discussion
See "General Meeting Discussion" below.

*Question 3.* *If we restart under a new protocol, would the FDA accept an Adaptive Statistical Plan?*

**Agency Response:**
**See our responses to Question 2. We recommend a new study with two treatment arms. Therefore, it may not be necessary to adjust the type I error rate for multiple doses. You may not need an adaptive design in the new protocol. However, if you prefer to use an adaptive design in your new protocol, provide the details in the protocol and Statistical Analysis Plan (SAP). We will provide comments upon review.**

Discussion
See "General Meeting Discussion" below.

*Question 4.* *If Lannett continues the current trial, what if any modifications or statistical conditions would FDA be interested in seeing?*

**Agency Response:**
**See our responses to Question 1. We recommend that you continue the current trial to complete collection of the remaining safety data, and we do not have additional recommendations for modifications or statistical conditions.**

Discussion
See "General Meeting Discussion" below.

*Question 5. Does the FDA have any additional recommendations for Lannett?*

**Agency Response:**
**Additional recommendations may be given after submission of a revised plan or protocol.**

Discussion
See "General Meeting Discussion" below.

Question 6. *Lannett requests that the FDA amend the existing Special Protocol Assessment (SPA) to reflect what is acceptable to the agency.*

**Agency Response:**

**As the efficacy portion of your trial is complete, the current Special Protocol Assessment cannot be amended.**

Discussion
See "General Meeting Discussion" below.

## General Meeting Discussion

The Sponsor distributed a handout entitled "Clinical Trial Protocol Issue List", dated January 4, 2015, containing five points for discussion with FDA. This handout is appended to these meeting minutes. The Sponsor stated that they have investigated the conduct of their current trial in order to determine the factors that led to problems with the trial, and have concluded that there were issues with the trial execution. The Sponsor stated they believe that, if they correct these issues with the trial execution described in points 1 through 4 on the handout, they can complete the trial successfully. The Sponsor read through the first four points on the handout, and asked the Agency for comments.

The Agency requested clarification on point 1, regarding the maximum amount of cocaine that would be administered if four pledgets were used. The Sponsor confirmed that the maximum would be 160 mg of cocaine if four pledgets were used at 1 mL of solution per pledget. The Sponsor added that, normally, usage is two pledgets per nostril and one nostril per procedure, although this can vary.

The Agency stated that, preliminarily, points 1 and 2 appear to be acceptable, but that points 3 and 4 may require some discussion.

For point 3, the Agency stated that, the interpretation of (b) (4) could be difficult for the Agency to interpret when evaluating the study results, in comparison to the use of a pain scale rating. The Sponsor stated that they are open to revising (b) (4), but believe that the pain scale is confusing to patients because they confuse pressure with pain when they are trying to assign a pain scale number. The Agency suggested that the Sponsor, in their protocol submission, propose several options for the standardized instructions for stating difference between pain and pressure and the Agency will review them. The Sponsor agreed to do so.

For point 4, the Agency stated that, in the new protocol submission, the Sponsor should be very clear about the waiting period and provide a rationale for the time proposal. Additionally, the Sponsor should clearly define, for treatment failures or placebo, what other types of anesthesia will be allowed (per standard practice), and make clear in the protocol what agents are to be considered not safe to allow as rescue. The Sponsor clarified that no additional cocaine is allowed per the protocol, but agreed to add clear definitions to the protocol of what other types of anesthesia will be allowed during the study.

The Sponsor stated that, for point 5 concerning Statistical Issues and Patient Numbers in Proposed New Protocol, the Agency should ignore the statements on the alpha test and adaptive

plan. The number of proposed patients in the handout is inaccurate and will need to be revised, but asked the Agency to clarify the number of exposures of 4% versus 10% required, as the original request was for (b) (4) exposures. The Sponsor plans to have exposures to the 4% cocaine in the efficacy portion of the new proposed study, and an equal number of exposures to 4% and 10% cocaine in the safety portion of the study, which includes the current study and the new proposed study. The Agency suggested that the Sponsor include in their proposal the total exposure numbers, and a detailed breakdown of where the numbers will come from (current study or proposed study) and from which treatment group (4% or 10% cocaine), when they submit the study protocol for review. The Sponsor agreed.

The Agency requested clarification of the Sponsor's statement that they plan to close the current study. The Sponsor clarified that they will stop the current study and complete the study report, which they plan to include in their future NDA submission. The Sponsor will send in a new protocol incorporating the changes discussed today with tracked-changes, within approximately two weeks.

**Additional General 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. In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions,

and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance for industry, *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf. 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

## 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 ).

## 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.

## 3.0 ACTION ITEMS

a) The Sponsor will send in a new, detailed, track-changes protocol incorporating the changes discussed today, within approximately two weeks.

b) The Agency agreed to review the protocol and provide comments if necessary.

## 4.0 ATTACHMENT: HANDOUT

Handout distributed by Lannett at the January 6, 2015, meeting:
Clinical Trial Protocol Issue List, dated January 4, 2015

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/s/

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DIANA L WALKER
01/29/2015