CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208969Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 124672

MEETING MINUTES

Amphastar Pharmaceuticals, Inc.
11570 6th Street
Rancho Cucamonga, CA 91730

Attention: Erik G. Poulsen, MS
Associate Vice President, Regulatory Affairs

Dear Mr. Poulsen:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Naloxone HCL for Intra-Nasal delivery (N002).

We also refer to the meeting between representatives of your firm and the FDA on November 5, 2015. The purpose of the meeting was to discuss the planned NDA for (b) (4) Naloxone HCL for Intra-Nasal delivery (N002).

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

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: November 5, 2015, 2:30 PM – 3:30 PM (Eastern)
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 124672
Product Name: Naloxone HCL for Intra-Nasal delivery (N002)
Indication: Emergency treatment of opioid overdose
Sponsor/Applicant Name: Amphastar Pharmaceuticals, Inc.

Meeting Chair: Sharon Hertz, MD; Division Director, DAAAP
Meeting Recorder: Diana Walker, PhD; Sr. Regulatory Project Manager, DAAAP

Amphastar Representatives	**Title**
Jack Zhang, PhD	CEO, Chief Scientific Officer (via telephone)
Jason Shandell, Esq	President
Mary Luo, PhD	COO, Chief Scientist (via telephone)
Diane Gerst	Executive Vice President, Corporate QA/RA
Tony Marrs	Vice President, Clinical Operations
Jing-Ni Ou, PhD	Clinical Scientist
Erik G. Poulsen	Associate Vice President, Regulatory Affairs
(b) (4)	
Pete Langosh	Vice President, Operational Improvement (via telephone)
FDA	**Title**
Sharon Hertz, MD	Division Director, DAAAP
Ellen Fields, MD, MPH	Deputy Director, DAAAP
Joshua Lloyd, MD	Clinical Team Leader, DAAAP
Elizabeth Kilgore, MD	Medical Officer, DAAAP (via telephone)
Daniel Mellon, PhD	Pharmacology-Toxicology Supervisor
Newton Woo, PhD	Pharmacology-Toxicology Team Leader
Carlic Huynh, PhD	Pharmacology-Toxicology 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)

Richard Chapman, PhD	CDRH Team Leader
Ryan McGowan, PhD	CDRH Reviewer
Yun Xu, PhD	Clinical Pharmacology Team Leader
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer
David Petullo, PhD	Biometrics Team Leader, Office of Biostatistics
Vicky Borders-Hemphill, PharmD	Team Leader, DMEPA
James Schlick, PharmD	Safety Evaluator, DMEPA (via telephone)
Bindi Nikhar, MD	Associate Director, Office of Combination Products
Steven Kinsley	Project Manager, OPQ
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

1. BACKGROUND

(i) (b) (4)

(ii) Naloxone hydrochloride (Naloxone HCl), an opioid antagonist, is the most frequently prescribed antidote for complete or partial reversal of opioid depression.

(iii) The proposed NDA submission will rely on the Agency's previous finding of safety and efficacy for the listed drug, Narcan (NDA 016636), and use comparative bioavailability data generated from a relative bioavailability (BA) study comparing the proposed product to a generic naloxone for IM injection, as the reference product, Narcan, is no longer marketed. Amphastar conducted their bridging study using two (2) generic products, Naloxone Injection 0.4 mg (Hospira, ANDA 070256), and 2 mg (Amphastar/IMS, ANDA 072076).

(iv) Amphastar met with the Division for a Pre-IND meeting on February 10, 2015, and opened an IND in March, 2015. The Sponsor was granted Fast Track Designation March 27, 2015, and obtained an Agreed PSP in October 2015.

(v) FDA sent Preliminary Comments to the Sponsor on November 2, 2015.

2. DISCUSSION

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.

Question 1. (b) (4)

(b) (4)

Amphastar proposes that the above trials are adequate to support N002 for efficacy and safety and that no additional clinical trials are required to support the NDA application.

Does the Agency agree with this proposal?

Agency Response:
We are concerned that (b) (4) is unlikely to be appropriate for the entire pediatric age range. If you cannot provide support for the proposed product in all pediatric age ranges (dose, volume, device), you will need to develop an age-appropriate formulation and then consider using that formulation for the entire pediatric age range to avoid having different products for different age groups.

We have the following additional comments:

a. **In the NDA, submit the partial AUC data (5 – 30 mins) analysis that you submitted in response to the information request in preparation for the PreNDA meeting.**

b. **Ensure that clinical site and bioanalytical data are robust and ready for inspection.**

c. **Confirm that the to-be-marketed product (naloxone formulation and device) was used in the clinical studies. If any changes are to be made or have been made from what was used in the clinical studies, submit the necessary studies or supporting data or information to bridge the products.**

d. (b) (4) **You will need to address this finding in your NDA.**

e. **Submit electronic datasets in SAS transport (*.xpt) format.**

Discussion
Regarding Comment 1d, (b) (4)

The Agency agreed that addressing this issue in the NDA is acceptable.

Question 2. (b) (4)

Agency Response:
The case reports may be submitted as supportive information in your application. However, the product used in those reports is a different formulation than the proposed product. Therefore, the applicability of those data to support the efficacy and safety of your product is limited. Accordingly, these data would not be appropriate for inclusion in labeling. The final labeling will be determined during the course of the NDA review.

Discussion
There was no further discussion of this question.

Question 3. (b) (4)

Does the Agency agree with this proposal?

Agency Response:
(b) (4) **However, these data would not necessarily preclude including other administration instructions with regard to body position (e.g., for patients to be placed on their back). We will review the data and the proposed labeling during the NDA review, and final labeling will be determined at that time.**

Discussion
The Sponsor asked for clarification on what is meant by "other administration instructions" (i.e., where in labeling this information would be communicated). The Agency stated that information regarding positioning of the patient for drug administration may be included in the Dosage and Administration section of the Package Insert, in addition to the Instructions for Use and any training materials.

Question 4. *Does N002 will be proposed as a kit containing two (2) single-use units to ensure adequate dosing for subjects requiring a second dose.* (b) (4)

Does the Agency agree with this proposal?

Agency Response:
We agree with co-packaging two dosing units in each kit to ensure that a second dose will be available when required in cases of an inadequate response, a device malfunction, or an administration error.

Discussion
There was no further discussion of this question.

Question 5. *In addition to the standard labeling, including the package insert, in order to facilitate user's ability to quickly* (b) (4) *administer the product, a user instruction guide for N002 has been designed and provided on the outside and inner lid of the kit box.*

Does the Agency agree with this approach?

Agency Response:
The placement of the user instruction guide with the kit appears reasonable. However, the acceptability of placement and usability of the user instruction guide will be a review issue.

Discussion
There was no further discussion of this question.

Question 6. *Informed by formative studies and the user risk analysis, Study* (b) (4) *was designed to serve as the formal Human Factors validation/summative study in support of proposed N002 kit that includes the user guide affixed to the kit box. The study was designed such that results can demonstrate that N002 can be used safely and effectively by the intended user population.*

Does the Agency agree with this proposal?

Agency Response:
We agree that data from a Human Factors (HF) validation study is required to support that your product can be used safely and effectively by users for the intended uses and environments. The acceptability of such data will be a review issue. Submit the following at the time of your NDA:

- **A summary of the results and analyses from the formative studies**
- **A discussion of changes made to your product after the formative studies, including how the results from the formative studies were used to update the user interface and use-risk analysis**
- **An updated use-related risk analysis for your product**
- **Human factors validation study report**
- **Labels and labeling that were tested in the summative human factors study**
- **Side-by-side comparison of intend-to-market IFU vs tested IFU, if differences exist**
- **Full description of any changes made to the user interface after completion of HF validation testing, along with rationale for the changes**
- **Three samples of product**

A preliminary review of your HF validation study results data identified some failures occurred that could have a negative impact on efficacy of the product, and you have not provided adequate justification for why further risk mitigation strategies should not be employed. Your submission described task failures during (b) (4) administration of the product. Any failures, difficulties, close calls, or subjective reports of problems with the user interface should be discussed with respect to whether they were caused by elements of the user interface, including labeling, and whether modifications are required to minimize risk. Residual risk associated with use that cannot be further reduced through modifications of the user interface should be discussed and a rationale provided for why it cannot be further reduced. If there are future plans to make changes to the user interface to further minimize risk, those changes should be validated in another human factors study.

Discussion
The Agency stated that, as it is very hard to complete formal training for everyone who may use this product, it is essential that the Sponsor address and correct the user errors that were seen in the Human Factors study. The Agency will rigorously assess the Human Factors study results

and ensure that the Instructions for Use are acceptable. User errors in a potentially life and death situation are unacceptable.

The Agency stated that calling 911 is not enough to constitute a risk mitigation strategy. The Sponsor should perform a root-cause analysis of failures and close calls to determine if the underlying user error issues were caused by elements of the user interface, including labeling, and if modifications are required. The Sponsor must then validate any changes made by conducting another Human Factors study.

The Sponsor agreed and stated that they are currently working on this issue. The Sponsor asked about the timeframe in which they could receive feedback if they were to do a root-cause analysis and conduct another Human Factors study, as they would like to submit the NDA as soon as possible. The Agency responded that they would do their best to provide timely feedback. The Agency stated that the NDA must be complete when it is submitted, unless they choose to request a Rolling Review submission. The Sponsor indicated that they would be interested in requesting a Rolling Review submission. In that case, the NDA is considered complete at the time the final piece is submitted. Refer to the guidance for industry: *Expedited Programs for Serious Conditions – Drugs and Biologics* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Question 7. *The sponsor will follow the Agency's instruction and related FDA guidance for CMC information to support the N002 NDA, specifically the FDA Guidance Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (July 2002). Further, three (3) month stability data generated in accordance with ICH Q1A(R2) for N002 at both accelerated (40° +/- 2° C) and controlled room temperature (25° +/- 2° C) will be available at the time of the expected NDA filing. Updated stability data for the six (6) month time interval will be submitted as it becomes available during the Agency review.*

Does the Agency agree that this CMC information is adequate to support the NDA filing for N002?

Agency Response:
No, we do not agree. Adequate stability data on at least three batches are necessary to be able to grant a commercially viable expiry dating period. It is expected that at least three batches of 6 months accelerated and 12 months controlled room temperature data will be submitted with the NDA.

Combination Products are subject to 21 CFR Part 4 Current Good Manufacturing Practice Requirements for Combination Products, available at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. As the combination product developer, provide data to demonstrate compliance with applicable provisions

based upon whether you select to use the streamlined approach or parallel approach. If you select the streamlined approach based on 210-211, we have provided general device development information within Attachment 2 of these preliminary responses to assist in demonstrating compliance with the applicable provisions for the device constituent part as applied to the combination as a whole. We consider that information generated to satisfy the requirements of the Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, in part, can be used to satisfy substantive elements of 21 CFR 820.30, *Design Controls*. We call particular attention to the additional advice Elements 2c and 2d, as they are essential to your demonstration of safety and effectiveness of the device constituent parts of the combination product.

Discussion

The Sponsor informed the Agency that they are ready to submit their NDA except that they do not have the required amount of accelerated stability data. The Sponsor proposed that they would request a Rolling Review and that the Agency consider extrapolating the expiry up to two times the length of available stability data, based on ICH guidelines. The Sponsor currently has one lot of 6 months accelerated data, three lots of 4 months accelerated data, and impurities and leachables data. Thus, the Sponsor is proposing to request a (b) (4) month expiry based on 6 months of stability data, and is asking for a deferral of the (b) (4) month real-time data until July 2016.

The Agency emphasized that the potential acceptance of 6 months of data at the time of NDA submission is unusual and that it might only be allowed given the public health priority for this type of product. The Agency stated that, if the Sponsor plans to submit only 6 months of stability data in their NDA submission, they should submit additional support from batches (b) (4) If the NDA is approved and additional stability data is obtained, the Sponsor can send in the data with the annual report.

The Agency reminded the Sponsor that, although they can request a Rolling Review submission, the review clock does not start until the final submission is received. At the time of the final submission of the Rolling Review NDA, the Sponsor must have at least 6 months of accelerated and long-term data on three batches; otherwise the NDA may not be filed.

Regarding the comments from the Agency concerning the device and combination product requirements, the Sponsor stated that they understand the combination product and device control requirements. The Agency pointed out that one important requirement for this type of product is a reliability analysis (as further described in Appendix 2) that includes information derived from testing the activation of a high number of devices over the entire shelf-life of the product. The Sponsor stated that they understood this requirement.

The Agency reminded the Sponsor of the concern over the (b) (4) product, which may not be appropriate for the entire pediatric age range. The Agency has previously advised the Sponsor to develop (b) (4) for the product. The Sponsor stated that they understand the Agency's point and will address it in the NDA submission.

Additional Nonclinical Comments

1. **Confirm with the DMF holder that the DMF for the** [redacted] (b) (4) **submitted to the Agency is active in status and is up-to-date.**

2. **New excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf. As noted in the guidance, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration*." (emphasis added).**

   - **Published literature to support the safety of an excipient 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 drug product formulation.**

   - **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 excipient. 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 novel excipient.**

   - **Safety justifications for oral drug products based on a compound being reported as generally recognized as safe (GRAS) in foods must be accompanied by appropriate reference to the Code of Federal Regulation, a discussion of any GRAS limitations, and an assessment of exposures typically obtained via food compared to the levels that will be obtained via your drug product when dosed up to the maximum daily dose. Maximum daily doses that exceed levels commonly consumed in foods are not supported by CFSAN GRAS determinations.**

3. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. 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 should be completed.**

       Refer to
       Guidance for Industry: *Q3A(R2) Impurities in New Drug Substances*
       http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

       and

       Guidance for Industry: *Q3B(R2) Impurities in New Drug Products*
       http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

    c. **Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at,**
       http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf.

4. **The NDA submission must contain information on potential leachables and extractables from the drug container closure system, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system should include specific assessments for residual monomers, solvents, polymerizers, etc. The choice of solvents and conditions for the extraction studies should be justified. The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, you should still evaluate at least three batches of your drug product**

over the course of your stability studies and base the final safety assessment on the 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, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, refer to the 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 and the FDA guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf. Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 1.5 mcg/day total daily exposure for a chronic indication or 120 mcg/day for an acute indication, or be adequately qualified for safety. 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.

5. **Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

6. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), 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, how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds, and 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.**

7. **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, you should conduct a thorough review 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.

8. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.**

9. **We may refuse to file your application if your NDA submission does not contain adequate safety qualification for any identified impurity that exceeds the recommended qualification thresholds or novel excipients that are not justified for safety or if the application lacks adequate safety justification for extractables and leachables from the container closure system.**

Discussion
There was no further discussion of these comments.

Question 8. *The Studies* [redacted] (b) (4) *were analyzed with Bioequivalence (BE) methodology to support the N002 NDA. If the SAS datasets are required for the N002 NDA submission, we plan to provide them as standard BE analysis datasets.*

Does the Agency agree that this is an acceptable approach?

Agency Response:
Yes, we agree. See comments under Question #1.

Discussion
There was no further discussion of this question.

Post-Meeting Notes:

1. The availability of other products with the same indication that you are seeking may have an impact on your submission. As an example, if the design of your product is such that it is less easy to use or has a more burdensome delivery in an emergency situation, (e.g. [redacted] (b) (4) compared to existing products)

the viability of your program may be in question if there isn't some compelling reason to offset these concerns, or data that the concerns are not warranted. We recommend that you consider any possible impact existing products may have as it may relate to a request for priority review, particularly the concept of unmet medical need (see Guidance for Industry, Expedited Programs for Serious Conditions –Drugs and Biologics, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf).

2. Since the drug product is meant for distribution and storage in locations such as police cars across the United States, for example, you must include testing of the drug product, stored at 4ºC and 40ºC, to the point of expiry, in your stability protocol.

3. ACTION ITEMS

a) The Sponsor stated that they understood that they must provide at least 6 months of stability data at the time of NDA submission.

b) The Sponsor stated that they will evaluate the human factors study results and perform a root cause analysis.

4. GENERAL 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.

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 *PLLR Requirements for Prescribing Information* websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

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

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

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

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

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

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

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
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.

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.

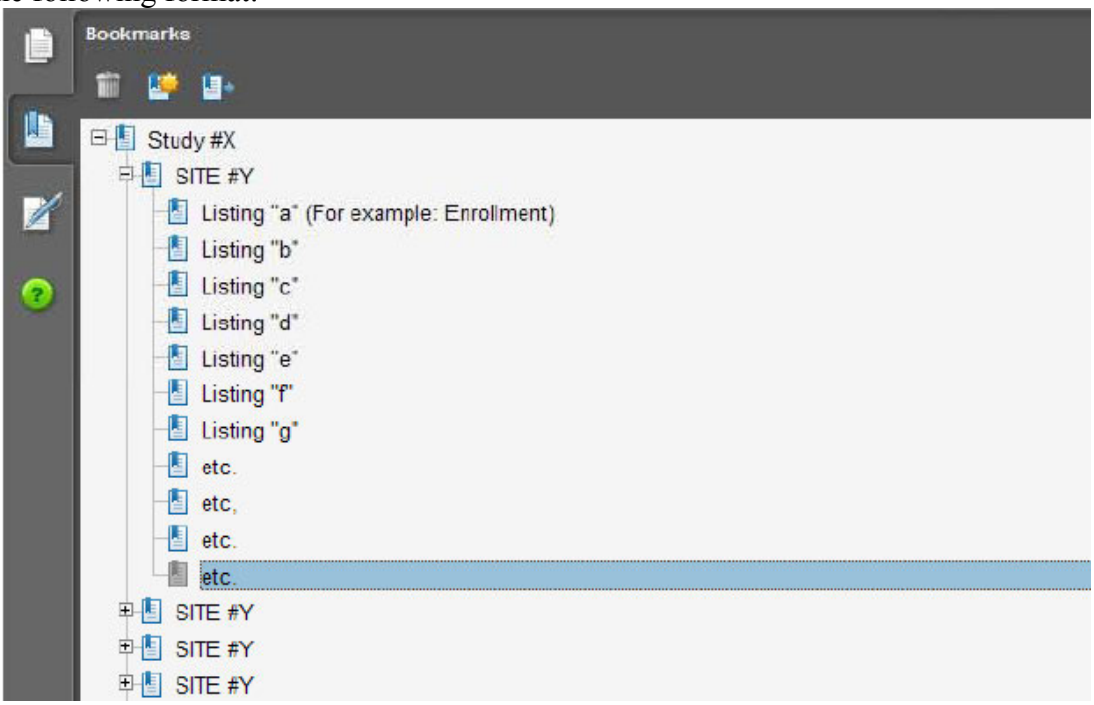
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

Attachment 2
Device Information

Based on information available about your proposed product, the Agency has provided the following advice to assist you in demonstrating compliance with medical device regulations:

1) Under the assumption that you will be choosing to pursue the drug CGMP-based streamlining approach outlined under 21 CFR 4.4(b)(1), you will need to provide additional information beyond typical drug CGMP regulation to demonstrate compliance with the following aspects of the Quality System regulation:

   - 21 CFR 820.20, Management Responsibility
   - 21 CFR 820.30, Design Controls
   - 21 CFR 820.50, Purchasing Controls
   - 21 CFR 820.100, Corrective and Preventive Actions
   - 21 CFR 820.170, Installation and 820.200, Servicing

2) With specific regard to21 CFR 820.30, Design Controls; it is probable that you already have a majority of information necessary to satisfy the intent of the regulation, either through internal device selection activities or formal design activities conducted by master file holders. However, as the combination product developer, it is your responsibility to properly document and show evidence of these activities to the Agency within the future NDA. In order assist you in demonstrating that the proposed combination product is designed within a state of control for purposes of the future NDA submission, the Agency has included the following templates and general advice:

   a. Combination Product Design Input and Design Output Information

      The Agency expects that you will present information within your future NDA submission that explicitly describes the attributes of your combination product that allow it to achieve the intended therapeutic effect. For each of these requirements, you should provide traceability to specific activities completed to verify or validate that the product achieves such effects. Note that some elements considered as "drug product specifications" under the *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation* Guidance will be relevant for this application. This may be communicated through a tabular format with accompanying report documents, such as the one shown for **example purposes** below:

Combination Product Requirement Name	Requirement Description/ Statement of Specification	Requirement Rationale	Verification or Validation Method	Verification or Validation Outcome	Reference to Section of Submission which Includes Actual Test Report or other Evidence Document
Spray Pattern and Plume Geometry Shape	Ellipsoid of relative uniform density	The elliptical shape was determined as the best option per Plume Geometry Exploration Studies	*Spray pattern shape test protocol summary*	PASS	SP-G_Verificiation_Protocol SP-G_Verificiation_Report
Spray Pattern and Plume Geometry Size	No axis is greater than 4.0 mm and the ratio of the longest to the shortest axes should be 1.00/1.30	The spray pattern dimension must be able to accommodate the 5 percentile nasal cavity size	*Spray pattern size test protocol summary*	PASS	SP-S_Verificiation_Protocol SP-S_Verificiation_Report
Spray Content Uniformity Attribute 1-N	…	…	…	…	…
Droplet Size Distribution Attribute 1-N	…	…	…	…	…
Combination Product shall not pose unreasonable toxicological risk	…	…	…	…	…
Combination Product shall be biocompatible	…	…	…	…	…
Combination Product shall be usable	…	…	…	…	…
Combination Product shall be reliable	…	…	…	…	…
…	…	…	…	…	…

b. Device Constituent Part Design Input and Design Output Information

The Agency expects that you will present information within your future NDA submission that explicitly describes the requirements of the device constituent part(s) of your combination product which are considered as critical to achieving the drug delivery attributes described in 2a, above. For each of these requirements, you should provide traceability to specific activities completed to verify or validate the requirements of the device constituent part. Note that some elements considered as characteristics of "container closure systems" under the *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation* Guidance will be relevant for this application.

This may be communicated through a tabular format with accompanying report documents, such as the one shown for **example purposes** below:

Device Constituent Part Requirement Name	**Requirement Description**	**Requirement Rationale**	**Verification or Validation Method**	**Verification or Validation Outcome**	**Reference to Section of Submission which Includes Actual Test Report or other Evidence Document**
Cannula Diameter	Cannula diameter =.5mm+.05mm	Cannula diameter is of this size achieves desired plume size	*Summary of verification tests*	PASS	Engineering_Drawings Dimensional_Verification_Protocol Dimensional_Verification_Report
Device Activation Force	Activation force <10N	Activation force low enough to allow device to be activated by pediatric user but is sufficiently high to prevent accidental activation	*Summary of verification tests*	PASS	AF_Verificiation_Protocol AF_Verificiation_Report
Device Color	Device colors shall be as described in drawing XYZ	Selection of color orange to enable ease of identification	…	…	…
…	…	…	…	…	…

c. Combination Product Risk Analysis

The Agency expects that you will present risk analysis information for the final-finished combination product. The risk analysis document should identify risks associated with the design and manufacturing processes of the combination product, should describe mitigations implemented to reduce these risks, and should provide rationale for any residual risks are considered as acceptable.

d. Analysis of Combination Product Reliability

The proposed intended use of your product involves the delivery of medication to treat a potentially life threatening condition. The environments of use and environments of storage are expected to vary greatly and the users of your product may have limited opportunity for alternative treatments. As such, the Agency believes that it is essential for your product to perform reliably. Please provide a reliability analysis for the subject combination product, including:

a. A statement of reliability requirements you have established for the subject product

b. Test reports or other studies that have been generated to verify reliability requirements. Verification of reliability requirements should be conducted after exposure to relevant pre-conditions, devices should be activated in the worst-case orientation, and products used for testing should be representative of final finished products. The Agency encourages future discussions on development of a reliability program protocol for the combination product.

Discussion

There was no additional discussion of the General Comments.

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

/s/

DIANA L WALKER
11/27/2015