CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210583Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105172

MEETING MINUTES

Recro Pharma Inc.
490 Lapp Road
Malvern, PA 19355

Attention: Diane P. Myers
Senior Vice President, Regulatory & QA

Dear Ms. Myers:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for N1539, injectable NanoCrystal colloidal dispersion meloxicam.

We also refer to the meeting between representatives of your firm and the FDA on January 19, 2017. The purpose of the meeting was to discuss the plan for the format and content of your NDA submission for N1539.

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 (240) 402-3158.

Sincerely,

{See appended electronic signature page}

Mavis Y. Darkwah, PharmD
Regulatory 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: January 19, 2017, 1:30 p.m. (Eastern)
Meeting Location: White Oak Building 22, Conference Room: 1315

Application Number: IND 105172
Product Name: N1539, injectable NanoCrystal colloidal dispersion meloxicam.
Indication: Management of moderate to severe pain
Sponsor/Applicant Name: Recro Pharma Inc.

Meeting Chair: Ellen Fields, MD, MPH, Deputy Division Director, DAAAP
Meeting Recorder: Mavis Darkwah, PharmD, Regulatory Project Manager, DAAAP

FDA Attendees	Title
Sharon Hertz, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Ellen Fields, MD, MPH	Deputy Division Director, DAAAP
John Feeney, MD	Clinical Team Leader, DAAAP
Timothy Jiang, MD, PhD	Medical Officer, DAAAP
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Jay Chang, PhD	Pharmacology/Toxicology Team Leader, DAAAP
Armaghan Emami, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, OCP
Kevin Krudys, PhD	Pharmacometrics Team Leader, Division of Pharmacometrics (DPM)
David Petullo, MS	Statistics Team Leader, Office of Biostatistics (OB)
Julia Pinto, PhD	Branch Chief, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Ciby Abraham, PhD	Acting Team Leader, ONDP, OPQ
Lawrence Perez, PhD	Drug Substance Reviewer, ONDP, OPQ
Karthik Iyer, PhD	Associate Director, OPQ
Priyanka Kumar, PharmD	Regulatory Health Project Manager, DAAAP
Jennifer Nadel, MD	Medical Officer, DAAAP

Mavis Darkwah, PharmD	Regulatory Health Project Manager, DAAAP
Sponsor Attendees	**Title**
Diane Myers	Senior Vice President, Regulatory and Quality
Randall Mack	Senior Vice President, Development
Stewart McCallum, MD	Chief Medical Officer
Vanessa Ragaglia, PhD	Senior Director, Toxicology and Patents
Christopher Barber	Senior Director, Quality
Alexis Gomez	Director, Clinical Project Management
Tu Tu	Senior Director, Regulatory
(b) (4)	Statistical Consultant
	Clinical Consultant
	Manufacturing Consultan (b) (4)

BACKGROUND

The Sponsor submitted a request for a Type B, Pre-NDA meeting on June 29, 2016, to discuss the plan for the format and content of their NDA submission for N1539 for the indication of management of moderate-to-severe pain.

The questions from the December 16, 2016, background package are shown in *italic font*. The Division responses are shown in **bold font**, and the discussion are in regular font.

FDA sent Preliminary Comments to Sponsor on January 18, 2017. After introductions, the discussion focused on Questions 1a, 1b, 7 (FDA response to Question 6), 10 (FDA responses 1 and 2), and Question 12.

DISCUSSION

Question 1a: The package of characterization data is provided in Section 1.10.2.1.2.6. Please comment on the acceptability of the characterization data provided to support filing of the NDA.

FDA Response
The evaluation of the characterization data will be conducted during the NDA review, and additional information may be required during the review. Expand your X-ray diffraction study to include the (b) (4) through manufacturing and storage. Additionally, perform dissolution studies on the drug product.

Discussion
The Sponsor clarified that the dissolution testing was performed as part of product development and that the results indicate dissolution is instantaneous. The Sponsor will submit the data as part of the NDA characterization package for Agency review.

Question 1b: A description of the particle size distribution methodology evaluated has been provided in Section 1.10.2.1.2.6. Does the Agency agree with Recro's decision to continue to report the Z-average/PdI values instead of a three tier distribution to control the finished product and to evaluate stability?

FDA Response
We agree that you may report the Z-average/PdI values instead of a three tier distribution. Note that you have supplied additional plot information for reference and supportive purposes. Additional validation will be expected at the time of NDA submission.

Discussion
The Sponsor clarified that the Malvern Zetasizer method has been validated to report the Z-average and PdI values, and was summarized in the validation report provided in the briefing document. The Sponsor inquired if additional validation reports that have not been addressed in the submitted validation report will be expected. The Division responded that the additional plot information for reference and supportive data provided in the meeting package does not need to be validated unless it is used to set a specific limit, and that the Division is interested in seeing all data used in evaluating the method. Therefore additional data should be included with the validation report.

Question 1c: Due to limitations experienced with laser diffraction and potential analyst subjectivity with the SEM summarized in Section 1.10.2.1.2.6, Recro does not plan to perform a complimentary routine analysis. Does the Agency agree with Recro's decision?

FDA Response
Complimentary routine analysis may not be needed to evaluate the finished product and product stability. Ensure during product development that the analytical method(s) chosen can measure quality consistency of the proposed commercial batch to meet all drug product release/stability specification limits. Method validation for all non-compendial methods will be expected at the time of NDA submission.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 2: The proposed analytical methods, commercial release, and stability specifications for the drug product are provided in Section 1.10.2.1.2.9 and Section 1.10.2.1.3 . Does the Agency agree with the proposal put forward for theses specifications?

FDA Response
For the release specifications, provide an orthogonal test for the identification of the API according to ICH Q6A. Acceptance criteria for Z-avg, PDI, osmolality, trace metals, and leachables must be provided at the time of NDA submission. The evaluation of the analytical methods, commercial release and stability specifications will be conducted during the NDA review.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 3: *A proposal to support expiration dating of four years is provided in Section 1.10.2.1.3. Does the Agency agree that the proposal is acceptable?*

FDA Response
Your proposal for requesting a 4-year expiry by submitting four batches of 48 months of stability data appears appropriate. The proposed expiry will be evaluated during the NDA review.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 4: *It is proposed* [redacted] *bulk meloxicam* [redacted] *batch size* [redacted] *to* [redacted] *API for commercial launch. Does the* Agency agree with the proposal put forward in Section 1.10.2.1.2.4 to support the inclusion of the [redacted] commercial batch size in the original NDA?

FDA Response
Your proposal appears to be acceptable. Additional information may be needed during the NDA review.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 5: [redacted] *Does the Agency agree with the data package proposed to support the alternative shipping container?*

FDA Response
Your proposal of an alternative shipping container as a post-approval change appears acceptable.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 6: *Due to the nature of this product, is a reduced AQL sampling plan acceptable for evaluating USP<790>, as provided in Section 1.10.2.1.2.8?*

FDA Response
We note that the drug product is an opaque, pale-yellow liquid, where a 100% visual inspection will not be possible according to USP <790>. The determination of whether a reduced AQL sampling plan is adequate for this product is dependent on the test method you propose. The determination of whether the test method and reduced AQL sampling plan is adequate will be determined during the NDA review.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 7: *Recro submitted EOP2 CMC responses to the Agency on 18 Nov2016 (Serial Submission #0071), Meeting minutes from the EOP2 meeting is provided in Appendix 1 and a copy of the responses from Serial Submission #0071 is provided as Appendix 2 for ease of review. Does the Agency agree with the positions provided in Serial Submission #0071?*

FDA Response
Our clarifications to Questions 6, 7, 8.2, and 8.3 from the August 26, 2015, End-of-Phase 2 meeting, and to your November 18, 2016 submission are noted below.

Question 6: **Include (b) (4) particle testing (b) (4) for the drug product.** (b) (4)

Question 7: **Determination of whether the extractable/leachable assessment is adequate will be determined during the NDA review. See the Additional Nonclinical Comments for further advice regarding the extractable/leachable assessment.**

Question 8.2: **Additional physicochemical property information has been provided and the evaluation of these data will be conducted during the NDA review.** (b) (4)

Question 8.3: **See our response to Question 1b.**

Discussion
The Sponsor discussed the Division's clarification to Question 6 (from the August 26, 2015, End-of-Phase 2 meeting) concerning (b) (4) particles. The Sponsor clarified that (b) (4)

Question 8: Does the Agency agree that the CMC package constitutes a complete package in support of the future submission of a marketing application?

FDA Response
Your CMC package appears adequate to support submission of the NDA from a CMC perspective. Additional information may be required during the NDA review.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 9: A summary of the nonclinical data collected to date, including data from studies requested at the EOP2 meeting is provided in Section 1.10.3. Does the Agency agree that the completed nonclinical program constitutes a complete package in support of the future submission of a marketing application? If not, what additional nonclinical studies are suggested?

FDA Response
The nonclinical program described in the meeting package appears appropriate to support filing your NDA. The final adequacy to support the approval of your product will be determined after a review of all of the data.

<u>Additional nonclinical comments</u>
We have the following additional comments for you to consider in deciding whether additional nonclinical information may be warranted for your NDA submission:

1. **We acknowledge that you have conducted extractables and leachables studies. However, the following updated comments reflect our most current thinking regarding**

Reference ID: 4585747

an adequate evaluation on potential leachables and extractables from the drug container closure system and/or drug product formulation to be submitted with an NDA. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for [redacted] (b) (4) **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** [redacted] (b) (4) **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 initial NDA 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., not more than 1.5 mcg/day or up to 120 mcg/day depending on the duration of treatment). However, from a general toxicology perspective, for parenteral products, 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:

a. **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**

b. **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**

c. **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.

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

b. **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 drug product formulation.**

c. **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 novel leachable**

2. **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 should be completed.

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

And

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

3. 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, and how these levels compare to ICHQ3A and Q3B 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. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.**

5. **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds, safety justification for a new or novel excipient, or safety characterization of extractables and leachables.**

6. **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.**

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. **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.**

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 10: A summary of the clinical data for the completed four positive Phase 2 and two positive Phase 3 studies, is provided in Section 1.10.4 as well as an update on ongoing clinical studies. At this time, does the Agency agree that the clinical program as described constitutes a complete package in support of the future submission of a marketing application? If not, what additional clinical data are suggested?

FDA Response
The completed clinical studies along with the on-going safety study appear sufficient to support filing of the NDA, in the absence of an unexpected safety signal from the ongoing

safety study. However, we have the following comments on your clinical development program:

1. **Based on Study REC-15-014 and the PK/PD modeling analysis, you selected a dosing regimen of 30 mg daily for the Phase 3 studies. As we commented before, simply demonstrating efficacy throughout the dosing period is not sufficient. While a 24-hour primary efficacy endpoint has been used as part of the data to support efficacy for parenteral products in the past, the 24-hour period represented multiple doses for those products. You must specifically demonstrate pain intensity relief during the second 12-hour period of the dosing interval. The two curves of PID versus time for the two Phase 3 studies both show no difference between study drug and placebo at 24 hours suggesting end-of-dose failure.**

2. **You have conducted two Phase 3 efficacy studies in different acute pain models. However, there are only 17 male subjects exposed to study drug in these efficacy studies. We remind you of our advice given in the first Type B, End-of-Phase 2 meeting, "…*efficacy must be demonstrated for multiple doses in a patient population that reflects the population intended for use of this product. Patients undergoing bunionectomy surgery may be suitable, however, you should note that this population is predominantly comprised of healthy females. You will therefore need to provide data to support why the efficacy is referable to male patients.*"**

3. **We also remind you of our prior comment "…*you are proposing the use of the study drug* (b) (4) *. However, subjects in the proposed Phase 3 efficacy and safety studies will only receive 2 or 3 doses. After 3 doses, meloxicam concentrations are not at steady-state. Meloxicam concentrations at steady state (Day 7) are 2.2- to 2.7-fold higher than those following a single dose.* (b) (4)**

Discussion
In response to the first comment, the Sponsor proposed to include secondary efficacy analyses of the 12-24 hour and 36-48 hour intervals in the study reports for the two Phase 3 efficacy studies. The Division agreed to the proposal and also recommended the Sponsor include an analysis of the last few hours of the 24-hour dosing period to assess the potential for end-of-dose failure.

(b) (4)

Question 11: A statistical analysis plan for an integrated summary of efficacy (ISE) is discussed in 1.10.4.4 and provided in Appendix 9. Does the Agency agree that the proposed statistical analysis plan is acceptable? If not, how does the Agency recommend that it be modified?

FDA Response
Yes, your plan is acceptable.

We note that your ISE focuses on a pooled analysis of all efficacy data. In the NDA, an ISE is more than just a pooled analysis. It is intended to compare the individual studies including an examination of study-to-study differences in results. You should explore the effect in subsets of the treated population, dose-response information from all sources, any available comparisons with alternative drugs, and any other information, so that the nature of the drug's effectiveness s can be as fully defined as possible, and the user of the drug can be given the best possible information on how to use the drug and what results to expect. Refer to the Guidance for Industry *Integrated Summary of Effectiveness,* available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf for more details.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 12: A statistical analysis plan for an integrated summary of safety (ISS) is discussed in Section 1.10.4.3 and provided in Appendix 10. Does the Agency agree that the proposed statistical analysis plan is acceptable? If not, how does the Agency recommend that it be modified? Specifically,

a. Case Report Forms (CRFs) and narratives will be provided for subjects who have a Serious Adverse Event (SAE) or discontinue the study due to an Adverse Event (AE). Narratives will be provided for subjects who have an AE of special interest. Does the Agency agree with the proposal? If not, what additional subjects should be included?

FDA Response
Your planed ISS with an integration of 11 studies seems to be acceptable. However, you did not specify how you are going to pool the 11 different studies. We suggest you include at least one pool for the three Phase 3 studies. Additional pools could include a pool of only the two Phase 3 efficacy studies and a pool of all controlled Phase 2 and 3 trials.

Discussion
The Sponsor clarified that the ISS will be based on 11 studies, however there will not be a data pool that includes all 11 studies. The Sponsor explained that there will be four pools of data which will include: 1) the four non-surgical studies; 2) all Phase 2 and Phase 3 surgical studies; 3) all Phase 3 surgical studies; 4) two Phase 3 efficacy studies. They also explained that subset

analyses will be performed for the pooled Phase 2 and Phase 3 surgical studies and will include the typical parameters (age, race, gender, concomitant medications, etc.). Also, selected subset analysis will also be performed in other pools as needed. The Division stated their agreement with the Sponsor's proposal, and also advised that if a signal is detected in the Phase 2 and Phase 3 surgical study pool, then subset analyses in the smaller pools should also be evaluated.

Question 13: Five legacy study reports and datasets have been generated by the previous Sponsor. Six studies have been conducted by Recro. A proposed plan, Section 1.10.6, outlines how these studies will be provided to the Agency in the NDA. Does the Agency agree with the proposed plan? If not, how does the Agency recommend that they be modified? Specifically,

a. *For the five studies completed by the previous Sponsor, Recro plans to submit raw and derived data used to generate the final Clinical Study Report (CSR) as well as SDTM and ADaM files with corresponding define.xml files. Does the Agency agree with this approach?*

FDA Response
Clarify whether the CSRs of the two efficacy studies, Study REC-15-015 and Study REC-15-016, were based on the raw and derived data instead of the SDTM and ADaM. Regardless, submit all programs used to derive the efficacy tables and figures presented in the CSR.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 14: Recro plans on filing an electronic NDA. Are there any specific format requests/requirements from this division that have not been addressed in the preceding questions?

FDA Response
Your planned electronic filing is acceptable. Since your IND consists entirely of paper submissions, all pertinent information from prior paper submissions must be included within the NDA. References to previous submissions are not sufficient.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 15: Along with the data that Recro has generated during development, Recro intends 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. Recro will establish that such reliance is scientifically appropriate, and data necessary to support any aspects of the proposed drug product that represent modifications to

the listed drug(s) will be provided in the application. Does the Agency agree with the proposed Regulatory submission pathway?

FDA Response
We generally agree with your proposal. To fulfill the 505(b)(2) regulatory requirements, you must establish a scientific bridge (e.g., via a comparative bioavailability study) between your proposed product and the each listed drug upon which you plan to rely on. The listed drug must be administered using its approved dosing regimen in the label in the comparative bioavailability study. Also see our general comments below on 505(b) (2) applications.

The systemic exposure of your product is higher than the listed drug with its highest approved dosing regimen, and it will accumulate after multiple doses resulting in even higher exposure. Therefore previous systemic safety findings of the listed drug, do not fully describe the systemic safety of your new product. In addition to reliance on the safety findings of the listed drug, provide data from additional studies and/or provide justification to support systemic safety of your product.

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

Question 16: Does the Agency have any comments, suggestions or recommendations regarding any aspect of the marketing application of N1539 that have not been addressed in the preceding questions?

FDA Response
Use the final to-be-marketed formulation in the clinical pharmacology and clinical safety and efficacy studies intended to support your NDA. Otherwise, you must provide adequate bridging information or justification why the study results using a different formulation apply to your final to-be-marketed product.

<u>Additional Clinical Pharmacology Comments</u>

1. **For the concentration dataset (.xpt), provide concentrations (including pre-dose concentration) of each analyte (where applicable), with information of treatment, dose, subject number, nominal time, actual time, sequence, period. The dataset should allow the Agency to conduct non-compartmental analysis using WinNonlin directly without any transformation of the dataset. Also include, age, sex, weight, and race for the subjects.**

2. **For PK parameters (.xpt), provide non-compartmental analysis PK parameters for each analyte (where applicable) for each subject with information of treatment, dose, subject number, sequence, period, etc. The dataset should allow the Agency to conduct bioequivalence (BE) analysis using WinNonlin and SAS directly without**

any transformation of the dataset. Also include, age, sex, weight, and race for the subjects.

3. **For your PK/PD modeling report (Study RECR-PCS-102), include datasets and model codes. All datasets used for model development and validation should be submitted as SAS transport files (.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates model, final model and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).**

Discussion
The Sponsor accepted the Agency's response. There was no further discussion.

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 PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

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

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

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 to sponsors/applicants 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), sponsors/applicants 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).

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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

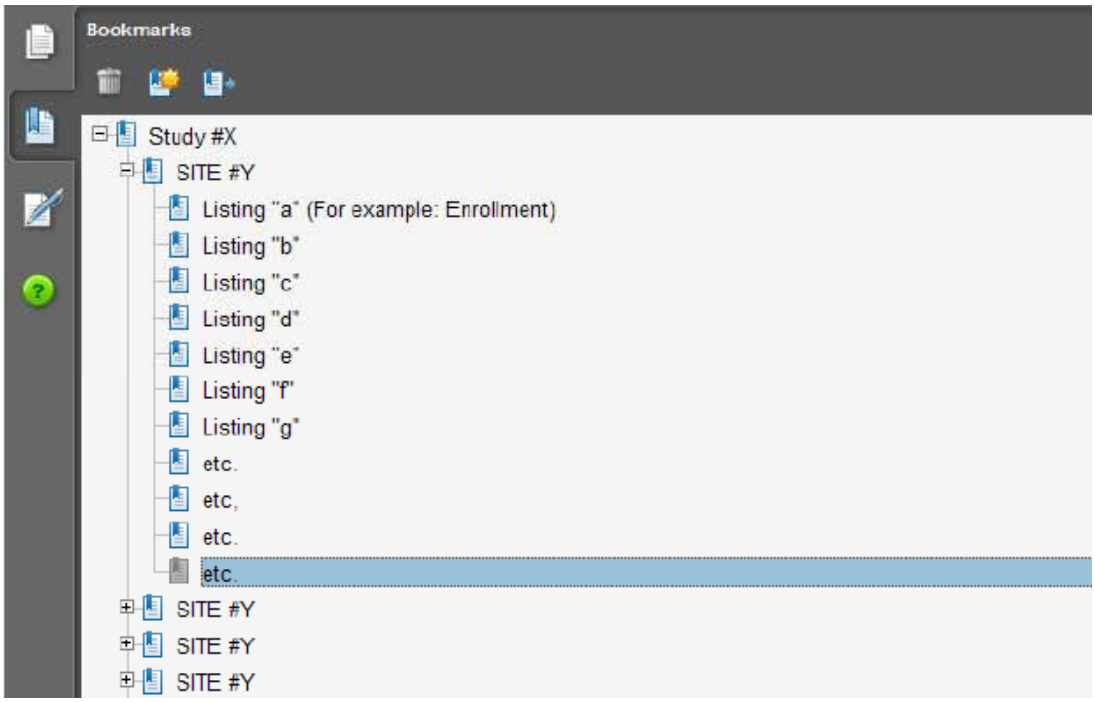
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, 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.

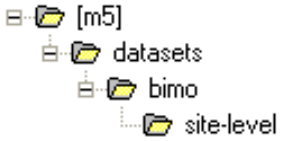
Attachment 1

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

ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

ACTION ITEM
The Sponsor will report the level of styrene in the finished product in the NDA submission.

ATTACHMENTS AND HANDOUTS
There were no attachments or handouts for the meeting minutes.

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

/s/

MAVIS Y DARKWAH
02/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105172

MEETING MINUTES

Recro Pharma Inc.
490 Lapp Road
Malvern, PA 19355

Attention: Diane P. Myers
Senior Vice President, Regulatory & QA

Dear Ms. Myers:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for N-1539, injectable NanoCrystal colloidal (b) (4) meloxicam (NCD Meloxicam IV).

We also refer to the meeting between representatives of your firm and the FDA on August 26, 2015. The purpose of the meeting was to seek the Agency's concurrence on the development plan and Phase 3 studies of N1539 in the management of moderate to severe pain.

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 (240) 402-3158.

Sincerely,

{See appended electronic signature page}

Mavis Darkwah, PharmD
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: 4585747

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: August 26, 2015, 3 p.m. (Eastern)
Meeting Location: FDA White Oak Building 22, Room 1313

Application Number: IND 105172
Product Name: N-1539, injectable NanoCrystal colloidal dispersion meloxicam (NCD Meloxicam IV)
Indication: Management of moderate to severe pain
Sponsor/Applicant Name: Recro Pharma Inc.

Meeting Chair: John Feeney, MD, Clinical Team Leader, DAAAP
Meeting Recorder: Mavis Darkwah, PharmD, Regulatory Project Manager, DAAAP

FDA Attendees	Title
Sharon Hertz, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
John Feeney, MD	Clinical Team Leader, DAAAP
Tim Jiang, MD	Medical Officer, DAAAP
Ciby Abraham, PhD	Acting Quality Assessment Lead,Office of New Drug Products(ONDP), Office of Pharmaceutical Quality (OPQ)
Eric P. Duffy, Ph.D.	Director, ONDP/DIVII
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Jay Chang, PhD	Pharmacology/Toxicology Team Leader, DAAAP
Armaghan Emami, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP2)
Suresh Naraharisetti , PhD	Clinical Pharmacology Reviewer, DCP2
Kevin Krudys, PhD	Pharmacometrics Team Leader, Division of Pharmacometrics (DPM)
Xiaofeng Wang, PhD	Pharmacometrics Reviewer, DPM
Freda Cooner, PhD	Biostatistics Team Leader, Office of Biostatistics (OB)

Feng Li, PhD	Biostatistics Reviewer, OB
Lisa Skarupa	Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Eva Yuan, PharmD	Regulatory Project Manager, DAAAP
Matthew Sullivan, MS	Chief, Project Management Staff, DAAAP
Mavis Darkwah, PharmD	Regulatory Health Project Manager, DAAAP
Sponsor Attendees	Title
Diane Myers	Senior Vice President, Regulatory and Quality
Randall Mack	Senior Vice President, Development
Christopher Barber	Senior Director, Quality
(b) (4)	Statistical Consultant
	Pharmacokinetic Consultant
Campbell P. Howard, MD	Medical Director
(b) (4)	Clinical Consultant
	Manufacturing Consultant
	Toxicology Consultant

BACKGROUND

Recro Pharma Inc submitted a request for a Type B, End-of-Phase 2 meeting on May 4, 2015, to seek the Agency's concurrence on the development plan and Phase 3 studies of N1539 in the management of moderate to severe pain.

The questions from the July 13, 2015 background package are shown in *italic font.* The Division responses are shown in **bold font,** and the discussion in regular font.

FDA sent Preliminary Comments to the Sponsor on August 25, 2015. After introductions, the discussions focused on Questions 1, 2, 3 (3.1 and 3.3), 4 (4.1, 4.2, 4.3, 4.11, 4.19, 4.20, 4.24, and 4.26), 7C, and 8.3. The Sponsor grouped the discussion under disciplines; Clinical, Nonclinical, and CMC.

DISCUSSION

Question 1: *Does the Agency agree that the nonclinical data package, as described, is adequate to support initiation of the Phase 3 studies of N1539 in subjects with moderate to severe pain following surgery? If not, what nonclinical studies are suggested to complete the package?*

Reference ID: 4585747

FDA Response

No, we do not agree. The nonclinical data package to date has not adequately evaluated the potential local toxicity of the proposed highest concentration of N1539 at 30 mg/mL. Therefore, you must conduct a repeat-dose intravenous local tolerance study of adequate duration (e.g., at least 3 days) in a single non-rodent species prior to initiating your planned Phase 3 clinical studies. In light of the particulate matter and cloudiness that was observed across a range of N1539 concentrations in the in vitro blood compatibility study, include full histopathological findings in this study to ensure that there are no toxicological consequences resulting from potential blood incompatibility of this formulation.

Discussion:

The Sponsor summarized the toxicological study that was previously filed to the IND and noted that these studies evaluated doses using a 25.5 mg/mL formulation and that there were no findings to report relative to site administration. The Agency pointed out that there is no supporting toxicology data for the proposed 30 mg/mL formulation a different product from the 25.5 mg/mL formulation and the increased concentration raises concerns for potential local tissue toxicity leading to vascular pathology, such as thrombi formulation with possible systemic consequences. The Agency stated that a repeat-dose toxicology study of at least 3 days will be needed to support the dosing regimen as currently proposed for the planned Phase 3 clinical study (b) (4) The Sponsor inquired if the repeat-dose toxicology study could be conducted in parallel with the planned Phase 3 clinical studies given the absence of local effects observed in toxicology studies performed with the 25.5 mg/mL formulation. The Agency stated that these studies were necessary to support the studies testing the 30 mg/mL concentration and they could not be done concurrently. The Agency informed the Sponsor that, pending supportive results, it would be acceptable to submit an audited draft study report of the repeat-dose toxicology study with a signed pathology report for local vascular tissue pathology and an in vitro blood compatibility evaluation, both testing the 30 mg/mL formulation, prior to initiating the Phase 3 clinical program. The final study report must be submitted within 120 days of the draft audited report.

The Agency inquired about the status of an ongoing bunionectomy study to which the Sponsor indicated that the current study in progress was a Phase 2 pilot study and that the protocol was submitted to the IND prior to initiation of the study. The Sponsor also indicated that humans were dosed with the 30 mg/mL drug product under this protocol. The Agency was unaware of the change and inquired if the 30 mg/mL product had the same composition and particle sizes as the 25.5 mg/mL product. The Sponsor responded that the drug product composition was the same, and that there were no changes in raw materials and the particle sizes were similar. The Sponsor also indicated that the change in drug product concentration was listed in the End-of-Phase 2 briefing document in 2010 and that the study protocol involving the 30 mg/mL drug product was submitted to the Agency. The Agency stated that an internal meeting will be held to determine if the ongoing Phase 2 study will need to be discontinued or put on hold.

Post Meeting Note: On August 27, 2015, the Agency notified the Sponsor that the continued use of the 30 mg/mL concentration was unacceptable and, on August 28, the Sponsor indicated that the ongoing Phase 2 study (REC-15-014) enrollment would be paused until a protocol

Reference ID: 4585747

amendment requiring the dilution of the study drug (30 mg/mL) to a concentration of 25.5 mg/mL was implemented. The Agency agreed to this proposal.

Question 2: *At this time, does the Agency agree that the completed nonclinical program, constitutes a complete package in support of the future submission of a marketing application? If not, what additional nonclinical studies are suggested?*

FDA Response

As noted above, for your NDA submission, you must conduct a 28-day repeat-dose toxicology study that addresses the safety of your to-be-marketed 30 mg/mL drug product per the ICH guidance for industry: *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf).

We have the following additional nonclinical comments regarding your development program:

A. For your 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 to support the proposed acute use indication.

Refer to guidance for industry: *Q3A(R2) Impurities in New Drug Substances*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf, and the guidance for industry: *Q3B(R2) Impurities in New Drug Products*, available at 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.

B. Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to ICH M7 guidance document titled: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk for the appropriate framework for identifying, categorizing, qualifying or controlling these impurities. This guidance is available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf.

Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.

C. Your NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for (b) (4), 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 or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many (b) (4) 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

Reference ID: 4585747

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, for your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for an acute indication, or be adequately qualified for safety. The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

D. We note that all NDA applications submitted after June 30, 2015, must include 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.

E. 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.

Discussion:
See Discussion to Question 1.

Question 3: *Does the Agency agree that the proposed Phase 3 program constitutes sufficient data to support a future marketing application submission for the management of moderate to severe pain? Specifically:*

Question 3.1: *Does the Agency agree that the proposed number of subject exposures described in Section 6.2.3 will be adequate to support the NDA submission?*

FDA Response
No, we disagree. As the Division commented previously in our Advice Letter dated September 28, 2009, because the systemic exposure to meloxicam is higher with N-1539 than with the reference drug at approved doses, the safety database must consist of at least 1000 subjects exposed to multiple doses of N-1539.

Discussion:

The Sponsor indicated that there are 900 multiple-dose exposures and that they can increase the number of subjects in the planned safety study in order to get to 1000 subjects exposed to multiple doses. They also noted that 270 of the subjects came from the previous sponsor's (Elan) study that used a 25.5 mg/mL concentration of the drug product, which is different from what will be used by the current Sponsor, but that the resulting dose is the same. The Agency agreed that the 270 subjects may be counted toward the total safety database of 1000.

The Agency stated that approximately 50% of the patients will need to be exposed to multiple doses of the highest dose (b) (4) The Sponsor indicated that, based on the feedback from the Agency, the plan for the Phase 3 study will need to be revised. The Agency requested to see an updated development plan for review.

Question 3.2: *Does the Agency agree that an adequately conducted bunionectomy study can serve as the pivotal "hard tissue" study to support the NDA submission? If not, what surgical population would be adequate?*

FDA Response
Bunionectomy is one of the appropriate surgical models to support efficacy for an acute pain indication.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 3.3: *Does the Agency agree that an adequately conducted abdominoplasty study can serve as the pivotal "soft tissue" study to support the NDA submission? If not, what surgical population would be adequate?*

FDA Response
Abdominoplasty may not be an appropriate surgical model for your study drug as we have concerns about wound heading and bleeding given the extensive nature of soft tissue damage during the surgical procedure. Provide support that use of an NSAID in this setting is acceptable.

Additionally, a surgical model is preferred that would permit evaluation of pain intensity over at least 48 hours.

Discussion:

The Sponsor indicated that there is wide range of abdominoplasty surgeries and that they will only enroll patients undergoing a mini-abdominoplasty (below the umbilicus) procedure, a procedure that limits the amount of soft tissue injury. The Agency responded that the proposed mini-abdominoplasty procedure seems like a reasonable approach to evaluate pain, and to mitigate risk of poor wound healing, bleeding, and hematoma formation. The Sponsor must have a predefined procedure on how to evaluate the severity of hematoma formation.

The Sponsor confirmed that the mini-abdominoplasty model will only require up to 3 days of dosing. The Agency pointed out that labeling will be based on the study data generated. (b) (4)

The Agency agreed that for the mini-abdominoplasty surgical model, the SPID-24 is acceptable for the primary endpoint as long as efficacy data is collected for 48 hours and SPID-48 is included as a secondary endpoint.

Question 4: *Does the Agency agree that the designs of the Phase 3 protocols, including proposed statistical analyses, are acceptable? Specifically:*

Study REC-15-015 (Abdominoplasty Surgery)

Question 4.1: *Does the Agency agree that the study population, as defined in the inclusion/exclusion criteria, reflects the target population and supports the proposed indication of management of moderate to severe pain? If not, what changes are recommended?*

FDA Response
See our response to Question 3.3.

Discussion:

See the Discussion under Question 3.3

Question 4.2: *Does the Agency agree with the proposed doses and dose regimen of 30 mg (b) (4)? If not, what changes are recommended and why?*

FDA Response
No, we do not believe you have adequately considered the results of your single-dose studies, along with the results of the dose-ranging study, in determining your proposed dosing regimens. Explore the potential for other doses and dosing regimens to provide a better response, while limiting adverse reactions. This was discussed at the previous EOP-2 meeting held on December 9, 2010.

For example, you have not explored the potential for a shorter dosing interval (e.g., BID dosing versus QD dosing) or a loading-and-maintenance-dosing regimen to sustain

efficacy over a 24-hour period. You have not described the potential benefit that would offset any additional risk associated with a daily intravenous administration of meloxicam with a higher C_{max} than the C_{max} following oral administration. (see response to Question 4.26).

(b) (4) However, subjects in the proposed Phase 3 efficacy and safety studies will only receive 2 or 3 doses. After 3 doses, meloxicam concentrations are not at steady-state. Meloxicam concentrations at steady state (Day 7) are 2.2- to 2.7-fold higher than those following a single dose.

(b) (4)

Discussion:

The Sponsor stated that QD dosing of 30 mg (b) (4) is being discussed but the final decision will not be made until after the PK/PD modeling is complete. They also stated that QD dosing will be more convenient for outpatient surgery. The Agency questioned the benefit of an IV NSAID versus oral analgesics before discharging a patient, to which the Sponsor stated that IV NSAIDS have a quicker onset and work well prior to discharging patients. (b) (4)

The Agency stated that the potential for BID dosing should be evaluated during the PK modeling. The Sponsor confirmed that BID dosing will be included in the modeling. The Agency also inquired if any comparator would be used in the Phase 3 study, and the Sponsor replied that placebo will be the only comparator. Dose-response and the possibility of a plateau effect with this drug was discussed. The Sponsor stated that a significant treatment effect was observed between the 30 mg and 60 mg doses in the dental pain study, to which the Agency responded that dental pain is historically more responsive to NSAIDS than some other surgical populations. The Agency confirmed that the use of the PK/PD modeling approach to select a dosing regimen for the Phase 3 study was acceptable. The Agency would like to review the results of the modeling when available.

Question 4.3: *For this population, does the Agency agree with the primary endpoint of $SPID_{24}$?*

FDA Response

No, the preferred primary endpoint is the sum of pain intensity difference (SPID) at 48 hours (see also our response to Question 3.3).

Discussion:

See the Discussion under Question 3.3. The Agency agreed that for the mini-abdominoplasty surgical model, the SPID-24 is acceptable for the primary endpoint as long as efficacy data is collected for 48 hours and SPID-48 is included as a secondary endpoint.

Question 4.4: *Does the Agency agree with the secondary endpoints listed in Section 8.2.1 in the draft protocol? If not, what changes are recommended and why?*

FDA Response
The proposed secondary endpoints are acceptable.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.5: *Does the Agency agree with the timing of the efficacy assessments outlined in Section 6.2 of the draft protocol? If not, what changes are recommended and why?*

FDA Response
The proposed timing of the efficacy assessments is acceptable.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.6: *Does the Agency agree with the safety assessments and timing of these assessments outlined in Section 6.3 of the draft protocol? If not, what changes are recommended and why?*

FDA Response
The proposed safety assessments and timing are acceptable.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.7: *Does the Agency agree with the proposed approach for handling missing efficacy data described in Section 8.3.3 of the draft protocol? If not, what would you propose and why?*

FDA Response
No. We do not agree with the proposed approach.

A. You propose to replace all the pain intensity scores after the first rescue use with the pre-rescue pain score (LOCF) for the primary efficacy analysis. This is not acceptable. Your method is based on an assumption that appears difficult to justify. You may employ this approach as a sensitivity analysis.

B. You may consider the sensitivity analysis you proposed, which carries the pre-rescue score forward to replace pain intensity scores collected within two hours following each rescue (W2LOCF), as your primary efficacy analysis. Additionally, include a sensitivity analysis that utilizes all pain intensity scores collected before and after each rescue use instead of imputing them.

C. Furthermore, specify how to handle missing data from subjects who discontinue the study early in the efficacy analyses.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.8: *Does the Agency agree with the proposed multiple testing strategy for managing the type I error rate described in Section 8.3.2 of the draft protocol? If not, what would you propose and why?*

FDA Response
Your proposed hierarchical testing procedure for the primary efficacy endpoint appears acceptable. However, should you intend to include claims for the secondary efficacy endpoints in the labeling, you must specify a strategy for controlling the study-wise overall Type I error rate.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.9: *Does the Agency have any other comments on the proposed data analysis and statistical considerations outlined in Section 8 of the draft protocol?*

FDA Response
You propose to include a term for analysis center in the model for the primary efficacy analysis. According to the draft protocol, it appears that analysis center could be a site with more than five randomized subjects or a unit of two or more small sites. Clearly specify how the analysis center will be defined in the protocol.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Study REC-15-016 (Bunionectomy)

Question 4.10: *Does the Agency agree that the study population, as defined in the inclusion/exclusion criteria, reflects the target population and supports the proposed indication of management of moderate to severe pain? If not, what changes are recommended?*

FDA Response
The study population is acceptable (also see our response to Question 3.2).

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.11: *Does the Agency agree with the proposed doses and dose regimen of 30 mg (b) (4)? If not, what changes are recommended and why?*

FDA Response
No, see our response to Question 4.2

Discussion:

See the discussion under Question 4.2

Question 4.12: *For this population, does the Agency agree with the primary endpoint of $SPID_{48}$?*

FDA Response
The sum of pain intensity difference (SPID) at 48 hours is an appropriate primary endpoint.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.13: *Does the Agency agree with the secondary endpoints listed in Section 8.2.1 in the draft protocol? If not, what changes are recommended and why?*

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FDA Response
The proposed secondary endpoints are acceptable. Include endpoints for total and average-daily opioid consumption.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.14: *Does the Agency agree with the timing of the efficacy assessments outlined in Section 6.2 of the draft protocol? If not, what changes are recommended and why?*

FDA Response
The proposed timing of the efficacy assessment is acceptable.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.15: *Does the Agency agree with the safety assessments and timing of these assessments outlined in Section 6.3 of the draft protocol? If not, what changes are recommended and why?*

FDA Response
The proposed safety assessments and timing are acceptable.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.16: *Does the Agency agree with the proposed approach for handling missing efficacy data described in Section 8.3.3 of the draft protocol? If not, what would you propose and why?*

FDA Response
See our response to Question 4.7.

Discussion:

No further discussion occurred.

Question 4.17: *Does the Agency agree with the proposed multiple testing strategy for managing the type I error rate described in Section 8.3.2 of the draft protocol? If not, what would you propose and why?*

FDA Response
See our response to Question 4.8.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.18: *Does the Agency have any other comments on the proposed data analysis and statistical considerations outline in Section 8 of the draft protocol?*

FDA Response
See our response to Question 4.9.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Study REC-15-017 (Major Surgery)

Question 4.19: *Does the Agency agree that the study population, as defined in the inclusion/exclusion criteria, reflects the target population? If not, what changes are recommended?*

FDA Response
For the safety study, the proposed target population, patients who undergo major elective surgery and are expected to require intravenous analgesia and remain in an inpatient setting for at least 48 hours, appears to be acceptable to support an evaluation of safety for use up to 48 hours.

Discussion:

See the discussion under Question 4.2

Question 4.20: *Does the Agency agree with the proposed doses and dose regimen of 30 mg* (b) (4) *? If not, what changes are recommended and why?*

FDA Response
See our response to Question 4.2

Discussion:

See the discussion under Question 4.2

Reference ID: 4585747

Question 4.21: *Does the Agency agree with the safety assessments and timing of these assessments outlined in Section 6.3 of the draft protocol? If not, what changes are recommended and why?*

FDA Response
The proposed safety assessments and timing are acceptable.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.22: *Does the Agency have any comments on the proposed data analysis and statistical considerations outlined in Section 8 of the draft protocol?*

FDA Response
Your proposal generally appears acceptable for an exploratory safety study in which no formal statistical inference will be conducted.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

General

Question 4.23: *It is anticipated that approximately 15%, 15% and 40% of the subjects enrolled in Studies REC-15-015, REC-15-016 and REC-15-017, respectively, will be males. Does the Agency agree that this constitutes a sufficient number of male subjects to support the NDA submission?*

FDA Response
The anticipated percentage of male subjects appears be acceptable.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.24: *The inclusion/exclusion criteria of the Phase 3 studies are designed to allow subjects with renal and hepatic insufficiencies to be enrolled into the studies. It is difficult to estimate the number of subjects with these insufficiencies that will be enrolled. Does the Agency agree that this approach is acceptable? If not, what would you propose and why?*

FDA Response
Designate a cohort in one of your three proposed studies to include high risk patients (greater than 65 years of age, GFR 60-89 mL/min/1.73 m^2).

Reference ID: 4585747

The exclusion criteria for liver function tests must be modified to exclude subjects with AST and ALT > 2.0 × ULN; AP > 1.5 × ULN; or total bilirubin> 1.2 × ULN.

Discussion:

The Agency stated that they would like to see PK data generated for the high risk, greater-than-65-year-old group, and that 10-15 patients alone in this age group would not be adequate to support product safety in this population. However, the Agency stated that if the Sponsor can demonstrate that the PK profile in this age group did not show a difference compared to the healthy younger subjects, then a smaller safety cohort may suffice.

The Sponsor expressed an interest in allowing their investigators discretion in determining the appropriate hepatic exclusion criteria. Some hepatic tests might be elevated due to particular surgical procedures and should not be exclusionary. Regarding both hepatic and renal exclusion criteria, the Agency disagreed with leaving these up to investigator discretion. However, statements in the clinical protocol could be specific and still outline criteria to allow enrollment of such patients. The Sponsor stated their understanding and their intent to add additional details to the protocol inclusion/exclusion criteria.

Question 4.25: *The inclusion/exclusion criteria of the Phase 3 studies allow subjects to be enrolled who are up to 75 years of age. It is anticipated that approximately <5%, <5% and 15% of the subjects enrolled in Studies REC-15-015, REC-15-016 and REC-15-017, respectively, will be ≥ 65 years of age. Does the Agency agree that this constitutes a sufficient number of elderly subjects to support the NDA submission?*

FDA Response
The anticipated percentage of subjects older than 65 is acceptable.

Also see our response to Questions 4.24.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 4.26: *The plan for a PK/PD analysis is provided in the Pharmacometric Analysis Plan (**Error! Reference source not found.**). Does the Agency agree that the pharmacometric analysis plan as described will be sufficient? If not what would you propose and why?*

FDA Response

No, we do not agree. The major objective of the population PK/PD analysis is to determine the optimal doses and dosing interval to be used in the Phase 3 trials. Therefore, this PK/PD analysis should be completed before finalizing the Phase 3 protocols and should support the dosing regimen(s) you plan to study. Refer to the meeting minutes of the Type B, End-of-Phase 2 meeting held on December 9, 2010, regarding our suggestion of using PK/PD analysis to facilitate the selection of final doses and dosing interval.

Additionally, you must use the final to-be-marketed formulation in the clinical pharmacology and clinical safety and efficacy studies intended to support your NDA for the proposed product. Otherwise, you must provide adequate bridging information or justification why the study results using a different formulation apply to your final to-be-marketed product.

Discussion:

See the discussion under Question 4.2

Question 5: *Results obtained from the evaluation of (b) (4) methods are provided in Section **Error! Reference source not found.**. Given that the Sponsor has shown that (b) (4) is not a suitable option for N1539, does the Agency agree that the current (b) (4) method is acceptable?*

FDA Response
We agree. The justification for (b) (4) processing with the supporting studies should be included in the NDA submission.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 6: *Historical (b) (4) particle testing is provided in Section **Error! Reference source not found.**. Based on material composition and the very low amounts of particles detected in batches to date, it is not intended to test for (b) (4) particles in commercial batches. Does the Agency agree with this approach?*

FDA Response
No we do not agree. There is not enough production history and batch data to adequately support the absence of testing for (b) (4) particles in the drug product commercial batches. Testing for (b) (4) particles should be included at the release testing of the drug product batches until sufficient data is obtained on commercial batches to demonstrate the absence of any (b) (4) particles.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 7: *Current drug product release and stability specifications are provided in Sections* ***Error! Reference source not found.*** *and* ***Error! Reference source not found.****, respectively. Does the Agency agree with the proposed release and stability specifications for drug product?*

FDA Response

The proposed specifications seem reasonable. However, you must also:

A. Provide a specification for osmolality.

B. Justify two different pH specifications for both product concentrations.

C. Propose a specification for the 5 identified leachables noted from the (b) (4) and provide a toxicological risk assessment to support the safety of the compounds at these specifications. If any of these compounds contain a structural alert for mutagenicity, they must not exceed 120 mcg/day for an acute indication, or be adequately qualified for safety from a genetic toxicity perspective. These leachables (b) (4) should be monitored by HPLC with validated methods. There is insufficient data provided in this submission to support the monitoring of these leachables by a GC method. Therefore, testing should continue on commercial batches, until sufficient data is obtained to support the absence of the leachables.

Additional comment

It is understood that pediatric studies are planned and will include newborns. Once the pediatric dosage is determined, reassess the endotoxin specification to ensure the potential endotoxin exposure remains within the USP recommendations.

Discussion:

The Agency stated the current GC method is not capable of detecting non-volatile extractables and strongly suggested that a LC/MS method would be more appropriate. The Sponsor responded that the results obtained for the leachables were very low and that they would provide the GC validation report for review.

The Agency also stated that (b) (4) for this type of manufacturing process and is concerned about (b) (4) particulates. The Sponsor responded that a validated method was used and that the particulate values were very low. The Agency stated that it is preferable that the (b) (4) particles were absent. The Agency also recommended that the Sponsor evaluate the current process and determine if the use of (b) (4) is feasible, to which the Sponsor responded that there are other approved products that uses (b) (4). The Agency acknowledged that although this is true, (b) (4) is not preferred.

Question 8: *Particle size characterization is provided in Section 10.3.1.4.11.*

Reference ID: 4585747

Question 8.1: *Based on the totality of the characterization work conducted to date and the particle size data provided, does the agency now consider the product to be a nano-formulation?*

FDA Response

The Agency does not have a regulatory definition for "nanotechnology" or related terms. Please refer to the finalized guidance for industry: *Considering whether an FDA-Regulated Product Involves the Application of Nanotechnology*, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM401695.pdf to determine if your product meets the points to consider outlined in that document.

We do not have a "nano-formulation" designation or a different review process for drug products that fall within the points-to-consider as outlined in the guidance. Instead, drug products containing nanomaterials proceed through the same regulatory pathway as drug products not containing nanomaterials.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 8.2: *Are there any additional considerations required prior to NDA?*

FDA Response

Per our response to Question 8.1, drug products containing nanomaterials are subject to the same regulatory pathway as drug products not containing nanomaterials. Products are evaluated on a case-by-case basis. The size, size distribution, and morphology (general shape and/or aspect ratio) of nanocrystals may impact the final product performance. Therefore, additional data on these attributes is typically requested. Further details on measuring size and morphology attributes may be found in our response to Question 8.3.

In addition, we recommend that you evaluate other attributes that may impact the quality of the product including, but not limited to:

(b) (4)

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 8.3: *Also, based on the data does the Agency agree that a three-tier particle size distribution is not required going forward?*

FDA Response

There are not enough data to determine whether a three-tiered particle size distribution is required going forward (b) (4) **The average particle size (Z-avg) may be interpreted incorrectly if the sample has a high pdi. Therefore, submit particle size distributions as well as histograms of samples to further characterize your particle size distribution**

In term of methodology, we recommend that complementary methods be used when measuring particle size and size distribution. Different instruments will often provide different endpoint measurements for size. Oftentimes, dynamic light scattering (DLS) is paired with a microscopy technique to further confirm and elucidate sizing results. We note you have used a field emission scanning electron microscope in STEM mode to conduct particle sizing analysis. D10, D50, and D90 of nanocrystal particles were provided. To assess the morphology of nanocrystals, provide representative images and a morphological description of the nanocrystals, and submit method validation reports for both STEM and DLS.

NCD Meloxicam IV is a nanocrystal formulation of meloxicam for intravenous administration. The in vivo performance of NCD Meloxicam IV will be sensitive to variations in nanocrystal particle size distribution. Therefore, a strict quality control strategy for particle size distribution is recommended (b) (4) **The method used to determine particle size distribution should be appropriately validated.**

Further, we note that the method listed in the release and specification tables is reported as " (b) (4) **". However, the particle size was measured on Malvern Zetazizer using a dynamic light scattering method.**

Discussion:

The Agency indicated that the PDI value for the particle size testing is high and may suggest a non-monodisperse distribution. The Sponsor agreed to provide particle-size distribution and histogram data, along with related STEM photos for review by the Agency.

Question 9: *Finished product stability summary is provided in Section* ***Error! Reference source not found.****. Does the Agency agree that the stability package provided, 3 batches of each strength (15 mg/mL and 30 mg/mL) at ICH conditions is sufficient to support NDA registration purposes?*

FDA Response

Yes, three batches of each strength, stored according to ICH conditions, are adequate for NDA submission. Note that at least 12 months of data are required for each batch in order to be able to grant a commercially viable expiry.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 10: *In-process bioburden limits were implemented to monitor the bioburden levels during process holding steps, details regarding the limits are provided in Section* ***Error! Reference source not found.*** *and Section* ***Error! Reference source not found.****, Description of the Manufacturing Process. Does the Agency have any additional comments/requirements pertaining to in-process bioburden analysis?*

FDA Response

The specification and sampling points appear to be adequate in the information provided. The final determination of the proposed bioburden testing will be evaluated during the NDA review.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 11: *A brief summary of the planned approach to study N1539 in pediatric subjects is provided in Section* ***Error! Reference source not found.****. Does the Agency agree with the outlined approach? If not, how does the Agency recommend it be modified?*

FDA Response

The outlined studies are acceptable. To fulfill the requirements of PREA, you must conduct PK, efficacy and safety studies for age birth up to two years. The efficacy for ages 2 through 16 years can be extrapolated from the adult efficacy in your Phase 3 study, but you must conduct PK and safety studies in this age group. These studies should be divided into three age groups (12 through 16 years, 7 through 11 years, and 2 through 6 years) that will be enrolled sequentially, with the oldest age groups studied first.

Discussion:

The Sponsor accepted the Agency's response. No discussion occurred.

Question 12: *Does the Agency have any comments, suggestions or recommendations regarding any aspect of the development of N1539 that have not been addressed in the preceding questions?*

FDA Response
We have no additional comments at this time.

Discussion:

No discussion occurred.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

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

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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.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.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

There were no action items.

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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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.

/s/

MAVIS Y DARKWAH
09/29/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20903

IND 105172

MEETING MINUTES

Elan Drug Delivery Inc.
1300 Gould Dr.
Gainesville, GA 30504

Attention: Roger Wayne Riley, R.Ph.
Senior Director, Regulatory Affairs

Dear Mr. Riley:

Please refer to your Investigational New Drug Application (IND) submitted April 9, 2009, received April 13, 2009, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Nanocrystal Colloidal Dispersion (NCD) Meloxicam.

We also refer to the meeting between representatives of your firm and the FDA on December 9, 2010. The purpose of the meeting was to discuss your Phase 3 development plans.

A copy of the official minutes of the meeting is attached 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) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Memorandum of Meeting Minutes
QT IRT Reference Document

Reference ID: 4585747

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	December 9, 2010
TIME:	1:30. pm to 2:30 pm
LOCATION:	FDA White Oak Campus Building 22 Silver Spring, MD
APPLICATION:	IND 105172
PRODUCT:	Nanocrystal Colloidal Dispersion (NCD) Meloxicam
INDICATIONS:	(b) (4) management of moderate to severe acute pain
SPONSOR:	Elan Drug Delivery, Inc
TYPE OF MEETING:	Type B, End-of-Phase 2
MEETING CHAIR:	Sharon Hertz, MD, Deputy Director, Division of Anesthesia and Analgesia Products (DAAP)
MEETING RECORDER:	Matthew Sullivan, MS, Regulatory Project Manager, DAAP

FDA Attendees	Title
Bob A. Rappaport, MD	Director, Division of Anesthesia and Analgesia Products (DAAP)
Sharon Hertz, MD	Deputy Director, DAAP
Timothy Jiang, MD	Medical Officer, DAAP
Pamela Horn, MD	Medical Officer, DAAP
Danae D. Christodoulou, PhD	CMC Lead, ONDQA
Jessica Cole, PhD	Microbiologist, Office of Pharmaceutical Science, New Drug Microbiology Staff
Aleksander Winiarski, PharmD	Safety Evaluator, Division of Pharmacovigilance II, Office of Surveillance and Epidemiology
Armaghan Emami, PhD	Pharmacology / Toxicology Reviewer, DAAP
Srikanth Nallani, PhD	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP II)
Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, DCP II
Dionne Price, PhD	Statistics Team Leader, Division of Biometrics II (DB II)
David Petullo, PhD	Statistics Reviewer, DB II
Matthew Sullivan, MS	Regulatory Project Manager, DAAP

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Sponsor Attendees	Title
Sharon Hamm, PharmD, RPh	Sr. Vice President, Technical Operations
Jeffrey D. Lazar, MD, PhD	President, Lazar Associates (Medical)
Elizabeth Vause	Clinical Operations & Project Management
Roger Wayne Wiley, RPh	Sr. Director, Regulatory Affairs
Carl Bauman, RPh	Director, Product Safety and Labeling
John Chippari	Associate Director, Regulatory Affairs
Michael Shaw, PhD	Associate Director, Non-Clinical
	(b) (4)
Mairead Fogarty	Sr. Director, Product Development

Meeting Objective(s): To discuss questions related to the Phase 3 development plans for NCD Meloxicam.

Opening Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the October 27, 2010, meeting package. Written comments were sent to the Sponsor on December 8, 2010. The Sponsor provided brief written responses on December 9, 2010, which are included below the applicable question.

NONCLINICAL QUESTIONS

Question 1: *Does the FDA agree that the following assessment justifies the adequacy of the highest dose tested in the hemocompatibility study, and that a safety margin has been established based on the data provided, and that no further hemocompatibility studies of NCD Meloxicam IV are required?*

Division Response:
Yes, we agree that no further hemocompatibility studies of NCD Meloxicam IV are required.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 2: *No further preclinical studies are proposed to support the Elan NDA for NCD meloxicam IV beyond those already conducted. Does FDA agree that the preclinical data package should be adequate to support a future NDA filing for the proposed indication?*

Division Response:
Yes, the nonclinical studies (28-day study in rats, 28-day study in minipigs, Ames assay and hemocompatibility study with NCD Meloxicam IV) along with reliance on

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prior findings of safety and efficacy for Mobic appear sufficient to support submission of the NDA.

Discussion:
There was no discussion beyond the Division's initial written response.

Additional Nonclinical Comments:

1. **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 in your NDA. 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 recommend 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 October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf . 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 challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf).**

   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 is scientifically appropriate.

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

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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 label.

4. **New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following http://www.bcg-usa.com/regulatory/docs/2005/FDA20055C.pdf.**

   As noted in the document cited above, "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).

5. **Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as described in the ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.**

   Adequate qualification would include:

   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. **Repeat dose toxicology of appropriate duration to support the proposed indication.**

6. **Genotoxic and carcinogenic impurities, or impurities that contain a structural alert for genotoxicity, must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative in vitro bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in the ICHS2A guidance**

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document titled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

7. **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 ICHQ3A and Q3B qualification thresholds along with a determination of whether the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.**

8. **The NDA submission must contain complete and definitive safety information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled "Container Closure Systems for Packaging Human Drugs and Biologics." The evaluation of extractables and leachables from the drug container closure system or from a transdermal patch product must include specific assessments for (b) (4), etc.). Based on identified leachables provide a toxicological evaluation 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). As many (b) (4) are known genotoxic agents, your safety assessment must take into account the potential that these impurities 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, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics" and "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation." Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at**

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http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf .

9. **Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment, may result in a Refusal-to-File or other adverse action.**

Discussion:
There was no further discussion on the additional comments.

CLINICAL QUESTIONS

Question 3: *Will FDA consider accepting the Dental Pain Study (N1539-02) as a pivotal proof of efficacy in support of a future NDA for the proposed indication?*

Division Response:
See our response to Question 4.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 4: *Assuming that the pattern of efficacy and safety observed to date in the open abdominal hysterectomy study (Protocol N1539-04) continues in the ongoing Cohort 2 group, will FDA consider accepting this study as a pivotal proof of efficacy in support of a future NDA for the proposed indication?*

Division Response:
The once daily dosing regimen that you have proposed for this product is unusual for a parenteral analgesic. While a 24-hour primary efficacy endpoint has been used as part of the data to support efficacy for parenteral products in the past, the 24-hour period represented multiple doses for those products. Furthermore, while the primary efficacy endpoint had been based on the first 24 hours, the studies continued to collect blinded efficacy data for as long as patients were in need of a parenteral analgesic. The abdominal hysterectomy study that you have described is not adequate to support a finding of multiple-dose efficacy for your proposed NDA, since the double-blind period for Protocol N1539-04 consists of just a single dose and since no additional blinded efficacy will be collected from this study. Results from this study can provide supportive evidence of efficacy for a single dose of NCD Meloxicam IV, as well as safety data for the duration of treatment that can supplement data from an adequate and well-controlled multiple-dose study.

Similarly, the dental pain study is not adequate to support a finding of efficacy for your product. The single-dose dental pain study may provide relevant information

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related to the behavior of the first dose of NCD Meloxicam IV, in terms of onset and duration of action and single-dose efficacy, however, it is not adequate to determine the efficacy of Meloxicam NCD for the treatment of acute pain over several days.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 5: (b) (4)

Division Response:
No. (b) (4)
(b) (4)
(b) (4)

Discussion:
The Sponsor stated that they wanted to ensure that they fully understood the Division's position. The Division explained that simply documenting that "(b) (4)" is used less in the Meloxicam arm of a study does not necessarily mean that the reduction is clinically meaningful. (b) (4)
(b) (4)

(b) (4)

The Division also clarified that a background opioid was not required. The Sponsor was also encouraged to seek agreement with the Division on their statistical analysis plan.

The Sponsor asked if an active comparator arm in a clinical study must be used "on label". The Division responded that it would be most appropriate to do so, but that as long as the product is used in a similar manner to the approved dosing and route of administration – and that it was considered within the standard of care – it may be acceptable to use the product off label.

Question 6A: *Will FDA consider accepting a robustly positive bunionectomy trial as a pivotal proof of efficacy in a model of post-surgical bone pain?*

Division Response:
As noted in response to Question 4, to support an acute pain indication for Meloxicam NCD, you must conduct an adequate and well-controlled, multiple-dose efficacy study in a population that reflects the intended population for use of this product. The primary endpoint for such a study must reflect multiple-dose efficacy, such as a SPID 48.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 6B: *Does the FDA feel that a reference comparator is necessary or desirable in such a study?*

Division Response:
While a reference comparator is not required, it can be useful for two reasons. First, if the study fails to demonstrate efficacy for your product, and also fails to demonstrate efficacy for an approved comparator, that indicates a failed study rather than a lack of efficacy for your product. Furthermore, it can be informative to see the effect size for your product relative to approved therapies. However, note that claims of superiority over a comparator require replicated evidence before they can be included in your labeling or promotional materials.

Discussion:
There was no discussion beyond the Division's initial written response.

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Question 6C: *Assuming that this study demonstrates a reduction in opioid use, similar to that described for Study N1539-04* (b) (4),

Division Response:
See our response to Question 5.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 6D: *In the event the data from Study N1539-04 demonstrates no relationship between Meloxicam plasma concentrations and pain relief, we would propose not to undertake the same approach to the collection of that data in Phase 3. Does the Agency agree?*

Division Response:
Since data, including the design, methodology and data analysis, pertaining to the relationship between NCD Meloxicam plasma concentrations and pain relief from Study N1539-04 were not available in the meeting package, we do not have enough information to comment on your proposal. In general, however, properly obtained exposure (or dose-) response information, collected where feasible, may provide additional insight into efficacy and/or safety aspects of the product.

Elan December 9, 2010, Response:

**** A review of the data from Cohort 1 in Study N1539-04 (referenced in Question 6D), has not demonstrated a relationship between plasma concentration and pain relief. This evidence can be further observed in the attached data provided herein. We will continue to evaluate the data from Cohort 2 in this regard; however, in anticipation of a similar outcome from the combined cohort 1 and 2 data, we would propose not to undertake the collection of plasma concentration data for the phase III program. Does the Agency agree?***

Discussion:
There was no discussion beyond the Division's initial written response.

Question 6E: *Assuming that the results from this study in a bunionectomy model provide clearly positive efficacy results and acceptable safety data, coupled with the positive findings from both the dental pain and abdominal surgery study, will these trials be considered sufficient evidence to support a future NDA for the proposed indication?*

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Division Response:
As stated in our response to Question 6A, efficacy must be demonstrated for multiple doses in a patient population that reflects the population intended for use of this product. Patients undergoing bunionectomy surgery may be suitable, however, you should note that this population is predominantly comprised of healthy females. You will therefore need to provide data to support why the efficacy is referable to male patients.

We recognize that you are studying a once-daily dosing regimen and have not yet decided the final doses to be carried forward into Phase 3. Looking at the PK profile of your product, it does not appear that the plasma levels are sustained throughout the 24-hour time period after dosing. Data from protocol N1539-04 seems to indicate that an 8-fold increase in dose from 7.5 mg to a substantially higher dose of 60 mg does not result in a corresponding improvement in efficacy indicating a shallow dose-response in this dose range. Furthermore, the duration of analgesia data from this study indicates that the effect may not be sustained for the full 24 hour period (mean of 17.7 hours in the meloxicam 60 mg group and mean of 12.5 hours for the 7.5 mg dose.) We suggest that you give careful consideration to these factors in deciding the final doses and dosing interval. You will need to specifically evaluate pain intensity during the second 12-hour period of the dosing interval to see if efficacy is sustained throughout the dosing interval.

Additionally, provide a rationale for why the person who administers the study drug is not blinded to the treatment group.

Elan December 9, 2010, Response:

** In Question 6E, we noted your query with regard to the continued demonstration of efficacy throughout the 24 hour dosing interval. Although the briefing package only addressed the time intervals of 0-12 and 0-24, an additional analysis of the time frame from 12-24 hours (as provided below) indicates that for 60 mg vs. placebo, the p value is <0.001; for the 7.5mg vs. placebo, the corresponding value is p=0.003. For the morphine vs. placebo in the same time interval the value was p=0.048. This would indicate that the duration of efficacy persists throughout the 24 hour interval for the NanoCrystal Meloxicam.*

SPID LS Mean	*60 mg*	*7.5 mg*	*morphine*	*placebo*
0-24 h	*-51734*	*-30515*	*-30962*	*-983*
12-24 h	*-20366*	*-10632*	*-7476*	*2402*

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SPID	*0-24 hours*	*12-24 hours*
60mg vs. Placebo	*P<0.001*	*P<0.001*
7.5mg vs Placebo	*P<0.001*	*P= 0.003*
Morphine vs. Placebo	*P<0.001*	*P=0.048*

** In Question 6E we further noted your comments regarding the PK profile and the corresponding correlations to efficacy. We believe these responses are very consistent with NSAIDs, as dose escalations historically have not resulted in directly related responses in efficacy as can be further seen in the references which follow:*

From the web site:
http://clinicalevidence.bmj.com/ceweb/conditions/msd/1108/1108_12.jsp

Gotzsche PC. Meta-analysis of NSAIDs: contribution of drugs, doses, trial designs, and meta-analytic techniques. Scand J Rheumatol 1993;22:255–260. Search date 1988. [PubMed]

Gotzsche PC. Review of dose–response studies of NSAIDs in rheumatoid arthritis. Dan Med Bull 1989;36:395–399. Search date 1985. [PubMed]

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** In light of the Agency's comments on the proposed bunionectomy phase III study, we are considering an alternative surgical procedure that would provide*

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broader patient group exposures. More specifically, we would propose a total knee replacement surgical model. Depending on the total number of patient exposures required for that study, we would consider supplementing it with either an additional post hysterectomy model or bunionectomy.

****Is the Agency aware of other surgical procedures that would provide the desired days (>5) on intravenous therapy?***

**** NanoCrystal Meloxicam is a colloidal yellow dispersion for which we have not been able to develop a suitable matching placebo. In lieu of the matching placebo, we have utilized an "unblinded administrator" for the Phase II study conduct, and would anticipate a similar approach for Phase III. We hope this clarifies your query in response to question 6E.***

Discussion:
The Sponsor stated that their analysis suggests that efficacy is demonstrated throughout the 24-hour dosing interval. The Division stated that the Sponsor needs to support the proposed dosing interval. Simply demonstrating efficacy throughout the dosing period is not adequate. The Division noted that the cited articles discuss chronic pain indications where lack of concentration-response may have been the case. The Division stated that the delayed effect (pain relief) noted may be analyzed better with advanced methodology, such as PK-PD analysis with delayed effect modeling rather than a direct concentration-response analysis as presented.

The Division suggested that the Sponsor make an attempt to understand the effect of body weight on drug disposition. The Division also noted that, although effect of body weight may not necessarily help with the adult clinical program, it may help with the future pediatric program.

The Sponsor stated that they plan to complete their current study and analyze the data before determining how to best proceed. The Division concurred with this approach.

The Sponsor asked the Division if a Total Knee Arthroplasty (TKA) model would be more appropriate than a bunionectomy model. The Division responded that perioperative NSAID use may be problematic for TKA patients, but that the Sponsor may be able to design a protocol that provides adequate safety. The Division also noted that issues such as wound healing and fluid shifts would have to be evaluated during the trial. The Division also responded that while safety data may be collected in an open-label fashion, blinded data is preferable.

The Division noted that the use of an "unblinded administrator" is acceptable.

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Question 7A: *A summary of expected patient exposures is provided. Will this provide an adequate number of exposures to support a future NDA submitted under section 505(b)(2)?*

Division Response:
Exposure of 531 patients to a single-dose and 403 patients to multiple doses with exposures typically from one to three days in duration is not adequate.

Since systemic exposure to NCD Meloxicam is higher than the exposure obtained with approved doses of the reference drug, we are concerned about toxicity beyond what is known from experience with the reference drug. In particular, we are concerned with renal toxicity in the setting of fluid shifts that can occur in the postoperative setting. Therefore, the safety database must consist of at least 1000 subjects exposed to study drug, with at least half exposed to multiple doses over the longest expected duration of treatment. The safety database must be based on use of the to-be-marked formulation of NCD Meloxicam. Clinical studies must allow up to seven days of dosing in those patients not yet converted to oral analgesics, in order to collect as much safety data as possible.

The size of the required safety database may increase if unexpected or serious safety signals arise during early clinical trials.

Patients undergoing bunionectomy surgery are generally predominantly female and relatively healthy. You will need to include patients in the safety database that have comorbidities such as renal or hepatic impairment, as well as elderly patients, in order to fully describe the safety profile of this product. It will also be necessary to collect data on hepatic and renal function, and possible negative effects of meloxicam on wound healing. Include an assessment of adverse events that occur after patients have been discharged home at four weeks post-discharge.

Discussion:
The Division stated that if the pharmacokinetic AUC is similar to the referenced oral product, than the Sponsor may not need 1000 patient-exposures. The Division stated the Sponsor could confirm with the Division the total number of patient-exposures necessary at the conclusion of their PK program.

Question 7B: *If not, what number of exposures (volunteers, patients, single doses, multiple doses) would the Agency expect for a future NDA submitted under section 505(b)(2)?*

Division Response:
See our response to Question 7A.

Discussion:
There was no discussion beyond the Division's initial written response.

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Question 7C: *As currently proposed, our overall clinical development program will have limited patient exposures typically from 1 to 3 days in duration. Will these exposures be considered suitable relative to a labeled indication for acute pain similar to that of Ketorolac: "Ketorolac tromethamine is indicated for the short-term (≤5 days) management of moderately severe acute pain....."?*

Division Response:
Provide a rationale regarding your plan to limit treatment with IV Meloxicam to 5 days. We note that Ketorolac has a limited duration of treatment due to safety concerns. Additionally, see our response to Question 7A.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 8: *Does the Agency have any further guidance regarding pediatric studies for this product?*

Division Response:
As stated in previous communications, a complete pediatric plan must be submitted prior to or at the time of the NDA submission. If you plan to request a waiver and/or deferral for certain age groups, these must be submitted with justification as to why the age groups should not be studied, or why studies should be delayed. Studies must include efficacy, safety and pharmacokinetics for pediatric patients less than two years of age, and safety and pharmacokinetics for patients age 2 to 17 years.

Since IV meloxicam will be administered in higher doses than the approved oral formulation, studies in pediatrics may be deferred until studies have been completed in adults and the safety profile in adults has been characterized.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 9: *Does the FDA agree that, the ECG monitoring conducted in the open abdominal hysterectomy study and the bunionectomy study will adequately address any issues of QT-prolongation with NCD Meloxicam IV?*

Division Response:
It is unclear from your question whether you have found information that raises the question of QT prolongation related to NCD Meloxicam IV. Provide any data that you have with regard to any possible QT issues with NCD Meloxicam. As the exposure to meloxicam with use of your product is expected to exceed the exposure

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of the product you plan to reference, a TQT study will likely be required for this application.

Elan December 9, 2010, Response:

In response to Question 9, please be advised that no QT issues have been observed within the Cohort 1 data set.

We further understand from your feedback that an increased exposure to meloxicam in excess of the currently approved oral dose will likely require the conduct of a TQT study. In the event that the exposure does not exceed that of the currently approved oral dose, does the Agency agree that a TQT study would not be required? If required to be conducted, can you provide some indication of the time frame for review of a Special Protocol Assessment (SPA)?

Discussion:
The Division stated that if the product has an AUC that is similar to, or higher than that of 30 mg of the oral product, then a TQT study must be conducted. However, the Division noted that if the AUC was close to that of a 15 mg dose, then a TQT study probably would not be necessary.

The Sponsor also requested clarification as to how long the Interdisciplinary Review Team will take to complete reviews of submitted Thorough QT (TQT) Study protocols. The Division stated that they would include the timeframe in a Post-Meeting Note.

Post-Meeting Note:
MAPP 6020.14 (http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082015.pdf) states that the IRT seeks to provide comments to the Review Division within 2 weeks of receiving a complete consult request for review of a TQT protocol. Additionally, the *QT IRT Reference Document*, which contains details of the required components for submission of a TQT protocol or study report, is attached to these meeting minutes.

CMC QUESTIONS

Question 10: *Elan developed the proposed stability matrix design shown in Tables 4 and 5 for stability testing consistent with the ICH Q1D guideline, for nine batches of drug product. The proposed matrix design is based on the satisfactory stability data generated to date, with a formulation containing the same excipients and the same API-to-excipient ratio (with the exception of sucrose), and with no change in the contact-surface materials. Refer to the background summary provided for additional detail.*

Does the Agency agree with Elan's matrix approach for the stability program, supporting product registrations?

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Division Response:
No, we do not agree. Your approach to use an intermediate concentration to support the lowest and highest strengths does not provide for sufficient bracketing. In addition, this is a high risk injectable product, the formulation is not a solution, and the drug substance has limited solubility; therefore the use of an abbreviated stability protocol is not advisable for your Phase 3 and registration stability batches.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 11: *Elan is proposing to manufacture the stability batches to support product registration at* (b) (4) *manufacturing scales as summarized herein. Does the Agency agree?*

Division Response:
(b) (4)

Elan December 9, 2010, Response:

**** In response to the comment provided for question 11,*** (b) (4)
(b) (4)

Discussion:
The Division stated that the Sponsor's December 9, 2010, response was adequate.

Question 12: *Elan selected a process* (b) (4) *to render the NCD Meloxicam IV drug product sterile. Does the Agency agree that* (b) (4) *is appropriate for NCD Meloxicam IV sterilization?*

Division Response:
No, the studies presented are not adequate to support the decision (b) (4)

You should continue to investigate the stability of your product after exposure to reduced processing conditions. For more information we refer you to the EMEA document entitled

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(b) (4)

Provide a three-tier particle size distribution for your formulation, e.g., D_{10}, D_{50}, D_{90}.

Elan December 9, 2010, Response:

**** In reference to the agencies response to Question 12, Elan proposes to use*** (b) (4) ***for Pivotal Phase 3 clinical supplies while continuing to evaluate*** (b) (4) ***we intend to proceed to commercial product manufacturing with the current*** (b) (4) ***process.***

(b) (4)

**** In response to Question 12, we would propose that the requested 3 point distribution of the particle size would be available at the time of NDA filling. Does the Agency agree?***

Discussion:
The Sponsor stated that they plan to enter Phase 3 studies using (b) (4) but to continue to evaluate (b) (4) The Division also noted that there may be a need to "bridge" the drug product

used in Phase 3 studies if it is not the same as the to-be-marketed product. For this reason, the Division stated that it would behoove the Sponsor to complete their evaluation (b) (4) as soon as possible, ideally prior to the start of the Phase 3 studies.

The Division also stated that the Sponsor should submit all relevant test data regarding particle size in the NDA submission, and that the particle size should be linked to drug product performance. The Sponsor inquired whether they needed to collect data through the stability cycle of the product. The Division responded that the Sponsor did need to do so, and that they should be aware of which critical attributes need to be monitored.

The Division also stated that there is a Guidance for Industry document in development which will contain additional information on nanoformulation development.

General Discussion:
The Sponsor stated that they may wish to adopt some adaptive design methodologies in their Phase 3 studies, and asked for the Division's opinion. The Division responded that the Sponsor should clearly specify the adaptations and statistical ramifications of the adaptations in the protocols. Review of the proposed adaptive design methodologies will be conducted in consultation with the Associate Director for Adaptive Design and Pharmacogenomics within the Office of Biostatistics. The Division also noted that it would include a link to the draft Guidance for Industry as a Post-Meeting Note.

> Post-Meeting Note
> The draft Guidance for Industry entitled *Adaptive Design Clinical Trials for Drugs and Biologics* is available via the following link:
> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf

Action Items:

1. The Sponsor will clarify their dosing interval and provided data supporting this determination.
2. The Sponsor will utilize appropriate endpoints in assessing the (b) (4) effect of their product. These endpoints may be discussed with the Division in the context of a Special Protocol Assessment.
3. A TQT study must be performed if the AUC of the product approaches or exceeds that of 30 mg/ day of the referenced oral product.

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QT IRT Reference Document

The QT Interdisciplinary Review Team (QT IRT) includes clinical, statistical, pharmacology, and clinical pharmacology reviewers, and project and database management.

The QT IRT is responsible for reviewing all thorough QT (TQT) protocols and completed QT studies, as well as protocols and results of studies intended to serve as alternatives to the TQT study. We are also available to respond to other QT-related questions.

I - In order for the QT IRT to review a **Thorough QT Protocol** and to accelerate the review process, the following items should be submitted:

- Electronic or hard copy of the study protocol
- Electronic or hard copy of the Investigator Brochure
- Statistical Analysis Plan
- A completed Highlights of Clinical Pharmacology Table (Table 1 shown below) – to be provided by sponsor.

II - In order for the QT IRT to review a **Thorough QT Study Report,** and to accelerate the review process, the following items should be submitted:

- Electronic copy of the study report
- Electronic or hard copy of the clinical protocol
- Electronic or hard copy of the Investigator's Brochure
- Annotated CRF
- Copies of the study reports for any other clinical QT study for this product that has been performed
- A Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files
- Please make sure that the ECG raw data set includes at least the followings: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, intervals (QT, RR, PR, QRS), HR, QTc [all corrected QT as end points, e.g. QTcF, QTcI (including individual correction factor), QTcB, or QTcN], Lead, ECG ID (link to waveform files if applicable).
- SAS code for the primary statistical analysis
- Data set whose QT/QTc values are the average of the replicates
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
- Narrative summaries and case report forms for any of the following that occur in this thorough QT study:
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study.
- Submission of the related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- A completed Highlights of Clinical Pharmacology Table (Table 1. shown below)

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Note: please submit all data sets in CDISC SDTM format if possible.

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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If the application is submitted electronically to the EDR, please provide the direct links to the above mentioned materials.

Also, please note that QT IRT goal is to provide a written response to consultation requests on:

- TQT or alternative study protocols (usually within 14 days of receipt of the complete information)
- TQT or alternative study reports (usually within 45 days of receipt of the complete information)

QT Interdisciplinary Review Team (QT IRT)

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

/s/

MATTHEW W SULLIVAN
01/25/2011

Reference ID: 2896437