CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213426Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128177

MEETING MINUTES

Laboratorios del Dr. ESTEVE, S.A.
15 Massirio Dr., Suite 201
Berlin, CT 06037

Attention: Rebecca Nortz
US Agent for Laboratorios del Dr. ESTEVE, S.A.

Dear Ms. Nortz:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Co-crystal E-58425.

We also refer to the meeting between representatives of your firm and the FDA on May 17, 2018. The purpose of the meeting was to discuss the proposal for an NDA submission for the indication "management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate".

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

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 17, 2018; 3:00 – 4:00 p.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: IND 128177
Product Name: Co-crystal E-58425 (Co-crystal of Tramadol and Celecoxib)
Indication: Acute pain in adults severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Sponsor Name: Laboratorios del Dr. ESTEVE, S.A.

Meeting Chair: Sharon Hertz, MD, Director, DAAAP
Meeting Recorder: Diana L. Walker, PhD, RPM, DAAAP

FDA Attendees	Title
Sharon Hertz, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Newton Woo, PhD	Pharmacology/Toxicology Team Leader, DAAAP
Kevin Snyder, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Michael Bewernitz, PhD	Pharmacometrics Reviewer, OCP
David Petullo, PhD	Statistics Team Leader, Office of Biostatistics (OB)
Julia Pinto, PhD	Branch Chief, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Donna Christner, PhD	Branch Chief, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Selena Ready, PharmD	DRISK Reviewer
Cameron Johnson, PharmD	DMEPA Reviewer
Sukhamaya (Sam) Bain, PhD	CMC Reviewer, ONDP, OPQ
Shalini Bansil, MD	Reviewer, Controlled Substances Staff
Erika Torjusen, MD, MHS	Clinical Team Leader, DAAAP
Diana Walker, PhD	Sr. Regulatory Health Project Manager, DAAAP

Sponsor Attendees (tentative)	Title
Carlos Plata Salamán, DSc, MD	Carlos Plata Salamán, DSc, MD. Chief Scientific Officer and Chief Medical Officer
Eduard Valentí, PhD	Regulatory Affairs Director & Pharmaceutical Quality Head
Neus Gascón, MD	Head of Medical Sciences and EU QPPV
Adelaida Morte, MD	Clinical Project Co-leader
Jesús Cebrecos, MD	Clinical Project Co-leader
Anna Vaqué, MD	Medical Drug Safety Officer
Mariano Sust, MSc, MD	Clinical Investigation Physician, Clinical Biostatistician
Empar Crespo, PhD	NME Regulatory Affairs Officer
Antonio Guzmán, PhD	Head of Toxicology
Gregorio Encina, PhD	Head of ADME and Bioanalysis
Carles Roquet	Quality Compliance Director (Esteve Química, S.A.)
Rebecca Nortz	Regulatory Affairs Manager, Breckenridge Pharmaceutical Incorporated (BPI)
Rob Falconer	Vice President, Technical Operations, BPI
Samrat Sisodia, PhD	Senior Director, Regulatory Affairs & Compliance, BPI

1.0 BACKGROUND

(i) The purpose of meeting is to agree on the regulatory path and content of an NDA submission for Co-crystal E-58425 (Co-crystal of Tramadol and Celecoxib).

(ii) Co-crystal E-58425 is formulated as an immediate-release tablet for oral administration containing a co-crystal of racemic tramadol hydrochloride and celecoxib.

(iii) The Sponsor proposes to submit a 505(b)(2) application that will rely for approval on FDA's finding of the safety and effectiveness of the two listed drugs (Ultram for tramadol hydrochloride and Celebrex for celecoxib, both of which are currently approved and marketed in the U.S.A. This will be a new fixed dose combination.

(iv) The Sponsor proposes the indication "management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate".

(v) A pre-IND meeting was held with the Agency on February 26, 2016, and the Sponsor has an Agreed PSP in place, dated August 2017.

(vi) FDA sent preliminary comments to the Sponsor on May 11, 2018. The Sponsor notified the Division of the questions upon which they would like to focus via an email on May 16, 2018, and provided handouts with discussion points (attached to these minutes).

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

2. DISCUSSION

Question 1: *The available non-clinical and clinical data show the potential of the Co-crystal E-58425 to be considered as a therapeutic alternative to address the nationwide public health emergency regarding the opioid crisis declared by the acting HHS Secretary on October 26th, 2017, which also supports the consideration of acute pain as an unmet medical need. Co-crystal E-58425 is more effective than available products as tramadol or celecoxib, and lower doses of tramadol show increased pain relief when administered in the Co-crystal E-58425. Based on this, the Applicant requests the Fast Track and the Priority Review designations for this novel Co-crystal E-58425. Does the FDA agree?*

FDA Response:
It is at your discretion to request fast track and priority review designations. You would need to submit requests with a rationale to support these designations. For fast track, the request should be submitted to the IND and you must provide evidence that E-58425 is intended to treat a serious condition along with nonclinical or clinical data that demonstrate the potential to address unmet medical need. For priority review, the request should be included in the NDA submission and you must provide evidence that the drug treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness over existing therapies. A determination of whether you qualify for fast track or priority review designation would occur after review of your request.

Refer to guidance for industry: *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf for additional information about fast track and priority review designations.

Discussion
There was no further discussion of this question.

Question 2: *Based on the Drug Enforcement Administration (DEA) classification for rac-tramadol hydrochloride and the results of ESTEVE-SUSA-101 study, the Applicant proposes that the Co-crystal E-58425 is classified as Schedule IV. Does the FDA agree?*

FDA Response:
A determination of the abuse potential of E-58425 and appropriate scheduling under the Controlled Substances Act will occur following submission and review of all the abuse-related information in the NDA.

Discussion
There was no further discussion of this question.

Question 3: *The Applicant intends to request a categorical exclusion for the submission of an Environmental Assessment for the Co-crystal E-58425 based on a non-increased use of both tramadol and celecoxib, as per 21CFR25.31(a). Does the FDA agree?*

FDA Response:
Your proposal appears reasonable. However, the final determination of whether your categorical exclusion is adequate will be determined during the NDA review.

Discussion
There was no further discussion of this question.

Question 4: *For the NDA submission and review, the ISE and ISS will include the data from the clinical studies sponsored by the Applicant, but not from the clinical studies sponsored by an independent third-party company and conducted outside the U.S.A. Does the FDA agree with this approach?*

FDA Response:
The integrated summary of efficacy (ISE) and integrated summary of safety (ISS) are detailed integrated analyses of all relevant data from clinical study reports, are required by the regulations, and should be located in Module 5.

For the ISE, you propose to provide integrated data from the Phase 2 clinical study ESTEVE-SACO4-201 and the Phase 3 clinical study ESTEVE-SUSA-301. Given differences in study design, your application should include a summary of the individual study results in addition to any integrated analyses.

For the ISS, you propose to provide integrated data from your Phase 1 studies (ESTEVE-SACO4-103, 102, 104, and 105 and ESTEVE-SUSA-101), your Phase 2 study in patients after oral surgery (ESTEVE-SACO4-201), and your Phase 3 study in patients after bunionectomy (ESTEVE-SUSA-301). You will not include studies performed by Mundipharma Research Ltd (MRL) in the ISS, but the serious adverse events from these studies will be included in the Clinical Summary of Safety. In general, your proposal appears reasonable, however, adequate safety data must be included in your NDA, including data from any source (foreign or domestic). If there are safety concerns identified in the studies performed by MRL, additional data may be requested to address these safety concerns.

Discussion
There was no further discussion of this question.

Question 5: *All non-clinical and clinical data from studies started after December 17th, 2016, including all studies conducted under IND 128177, are in conformance with the required data standards specified in the FDA Data Standards Catalog and the Technical Rejection Criteria for Study Data Document. For a number of studies started before December 17th, 2016 some data are not in conformance with such standards. The Applicant considers that this situation fulfills the requirements for data standards for NDA filing. Does the FDA agree?*

FDA Response:
We agree. Note that the traceability of the study results is critical regardless of the data standards.

Discussion
There was no further discussion of this question.

Question 6: *The Applicant considers that the analysis of the Co-Crystal E-58425 study data has not identified any new safety issues or trends beyond the existing data on tramadol and celecoxib, or any other features that would warrant an Advisory Committee meeting convened by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for the Co-crystal E-58425 during the NDA review. Does the FDA agree?*

FDA Response:
A final determination of whether to convene an Advisory Committee meeting will be made after submission of your application. Given that E-58425 is a combination of celecoxib and tramadol, an opioid analgesic, we anticipate that your application will be discussed at an Advisory Committee meeting to obtain input from outside experts and the public.

Discussion
There was no further discussion of this question.

Question 7: *The Applicant considers that:*
7.1 Co-crystal E-58425 is a co-crystal according to the Guidance for Industry "Regulatory Classification of Pharmaceutical Co-crystals"

FDA Response:
Yes, we agree. E-58425 appears to be a co-crystal according to the Regulatory Classification of Pharmaceutical Co-crystals guidance.

7.2 Co-crystal E-58425 is to be classified as a new type 4 combination of rac-tramadol HCl and celecoxib

Does the FDA agree?

FDA Response:
Yes, we agree that as per MAPP 5018.2, E-58425 would be classified as a Type 4 New Combination NDA.

Discussion
There was no further discussion of this question.

Question 8: *The Applicant proposes to use* (b) (4) *as the established name for the Co-crystal E-58425. Does the FDA agree?*

FDA Response:
We do not agree. The established name should be "(Celecoxib and Tramadol) tablets".

Discussion
The Sponsor provided background information and rationale in the meeting handout to support their argument (b) (4)

The Agency stated that this question has been discussed with the naming policy group, as well as taking into consideration the February 2018 Guidance on this topic, and the conclusion is that (b) (4) cannot be part of the established name. The Agency recommended that, (b) (4) should be handled through labeling. The Sponsor should propose language in Sections 11, 12 and 14 that accurately describes (b) (4)

Question 9: *9.1 - The Applicant proposes to submit 6-month ICH stability data at both accelerated and long-term conditions from the three Drug Product primary stability batches* (b) (4)

Does the FDA agree with this approach?

9.2 – If not, will the FDA accept the (b) (4)

NDA submission?

FDA Response:

No, we do not agree. The NDA is expected to be complete at the time of submission and should provide at least 6 months of accelerated and 12 months of long-term stability data on 3 batches of the drug product packaged within each of the to-be-marketed packaging systems. Any additional supportive data may be submitted within the first 30 days after NDA submission. We cannot guarantee review of any additional data submitted after the filing period.

Discussion
There was no further discussion of this question.

Question 10: *A DMF for Co-crystal E-58425 Drug Substance, containing CMC information, will be submitted to the FDA on the same day of NDA submission.*

10.1 - In this DMF, the Applicant proposes to select as regulatory starting materials of Co-crystal E-58425 Drug Substance, the starting materials of both tramadol HCl and celecoxib, as described in their respective DMFs. Does the FDA agree with the proposed selection of regulatory starting materials for the Co-crystal E-58425 Drug Substance?

10.2 - In this DMF of Co-Crystal E-58425 Drug Substance, the Applicant proposes making reference to tramadol HCl DMF # (b) (4) *and celecoxib DMF #* (b) (4) *instead of describing therein the manufacturing and control of tramadol HCl and celecoxib. Letters of Authorization (LOA) to both DMFs will be included in the DMF of Co-Crystal E-58425 Drug Substance, in eCTD Module 1, section 1.4.1 "Letter of Authorization". In addition, in the eCTD of NDA submission of Co-crystal E-58425, references to Co-Crystal E-58425 Drug Substance DMF, tramadol HCl DMF #* (b) (4) *and celecoxib DMF #* (b) (4) *will be made in section 3.2.S, and LOA to the three DMFs will be included in Module 1, section 1.4.1 "Letter of Authorization". Does the FDA agree with this proposed submission approach for manufacturing and control description and data of either Co-crystal E-58425 Drug Substance, tramadol HCl and celecoxib?*

FDA Response:

10.1: We agree with your selection of the starting materials.

10.2: We agree with your NDA submission approach of referencing DMFs for tramadol HCl, celecoxib and E-58425. However, the NDA CTD modules should also include summaries of critical information on the drug substance, including general information, manufacture, characterization and potential impurities, specification, test methods and their validation or verification at the drug product facility, reference standards used at the drug product facility, container closure system and stability.

Discussion

There was no further discussion of this question.

Question 11: *The Drug Product batches used in the three primary stability batches and in the clinical trial supplies batch manufactured for both the Phase 3 clinical study ESTEVE-SUSA-301 and the Phase 1 clinical study ESTEVE-SUSA-101 are representative of all the relevant batches described in the NDA. The Applicant proposes to submit in section 3.2.R of the eCTD the Executed Batch Records for:*
• The three Drug Product primary stability batches.
• The clinical trial supplies batch of bulk Drug Product manufactured for both the Phase 3 clinical study ESTEVE-SUSA-301 and the Phase 1 clinical study ESTEVE-SUSA-101, with the exception of either Executed Batch Records for over-encapsulation of Drug Product or Active Comparators for clinical trial blinding or for placebo manufacturing, which will not be included.

Does the FDA agree with this approach?

FDA Response:
Your approach appears to be acceptable.

Discussion
There was no further discussion of this question.

Question 12: *Does the FDA agree that the conducted regulatory toxicology studies with the Co-Crystal E-58425 are sufficient to support the NDA for the proposed indication?*

FDA Response:
The toxicology studies you have conducted to date appear adequate to support filing your NDA submission for the proposed indication. However, the adequacy of these toxicology studies to support approval of your drug product will be determined upon review of your final study reports submitted to the NDA. We note that the specifications for celecoxib-associated Impurity (b) (4) and tramadol-associated Impurity (b) (4) exceed the drug substance impurity qualification thresholds in ICH Q3A(R2) and will need to be tightened to NMT (b) (4) % or otherwise justified by additional qualification data (see Additional Nonclinical Comments).

Discussion
There was no further discussion of this question.

Question 13: *The Applicant plans to submit the data from the clinical studies conducted under the IND 128177, including the factorial design Phase 3 study ESTEVE-SUSA-301, which objectives have been achieved according to the Applicant's own assessment. Does the FDA agree on the completeness and suitability of the*

current clinical program for acceptability for NDA submission, filing, review and eventual approval?

FDA Response:
From a clinical perspective, we agree that the clinical program appears acceptable for NDA submission. Whether the submitted data are adequate to support filing and approval will be a review issue.

From a clinical pharmacology perspective, it appears that you have obtained tramadol, M1 and celecoxib relative bioavailability, single- and multiple-dose, and food effect information for E-58425.

We remind you that the final to-be-marketed product must be used in clinical and clinical pharmacology studies to support the NDA submission and labeling language. Otherwise, adequate bridging data or justification will need to be provided to demonstrate why data from a different formulation can be used to support your final to be marketed product.

For dosing recommendations regarding special populations, drug interactions, etc., see Clinical Pharmacology Response to Question 18.

Discussion
There was no further discussion of this question.

Question 14: Does the FDA agree with the proposed indication for the Co-crystal E-58425 "short-term (no more than 14 days) management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate"?

FDA Response:
The proposed indication will be a review issue. In general, your clinical program appears reasonable to evaluate the use of E-58425 for acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. If you intend to propose a limitation in terms of the number of days of use, provide a discussion of the rationale for the proposed duration. We note that the longest duration of use for E-58425 in your clinical studies was 7.5 days (15 doses) in study ESTEVE-SACO4-105 in healthy individuals. In your rationale, consider the duration of your clinical studies and other relevant clinical data that support your proposal.

Discussion
The Sponsor asked the Division for a recommendation for criteria that could be used to establish the number of days (limitation of use) that should be included in the indication. The Division stated that, as the number of days is not required to be included in the indication, the Sponsor should include a limitation of use if a limitation is supported with data or other rationale.

Question 15: *The Applicant plans to submit compiled adverse reactions from clinical studies in the corresponding section of the labelling (ADVERSE REACTIONS). Moreover,* (b) (4) *Does the FDA agree?*

FDA Response:
While specifics regarding the labeling of your product will be a review issue, we anticipate that the proposed product label will include safety information from the listed drugs and the completed clinical studies. We do not agree (b) (4)

Discussion
There was no further discussion of this question.

Question 16: *As discussed in the Pre-IND meeting, the Applicant proposed not to submit a REMS for this 505(b)(2) NDA, based on the well-known safety profile of either tramadol or celecoxib for an acute indication. However, based on the recent 2017 FDA Actions on REMS for Opioid Analgesics, the Applicant now proposes to submit a REMS containing all necessary elements for safe use in accordance to the recommendations from FDA for IR opioids in short-term use. Does the FDA agree?*

FDA Response:
A risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Therefore, you will need to submit a proposed REMS with your application. Although the final determination will be made during the course of the review, at this time we agree with your decision to join the shared system Opioid Analgesic REMS that that is currently under development.

Discussion
There was no further discussion of this question.

Question 17: *The Applicant considers that there are no scientific evidence or medical reasons to support that the abuse potential of Co-crystal E-58425 should be higher than the established risk profile of tramadol alone. Moreover, the pharmacokinetic characteristics of tramadol produced by the Co-crystal E-58425 (due to the co-crystal mechanism) also support that the abuse potential of Co-crystal E-58425*

would not be higher than the established risk profile of tramadol alone. In addition, abuse has not been reported with celecoxib, and neither there is an increase of adverse events or potentiation of adverse events with Co-crystal E-58425 compared to tramadol alone. Therefore, the Applicant does not plan to conduct abuse potential studies. Does the FDA agree?

FDA Response:
We agree that no abuse potential studies need to be conducted at this time for E-58425.

You should document adverse events (AE) associated with potential abuse and overdose for all Phase 1, 2 and 3 studies. Case narratives of each of these AEs should be provided, along with any serious AEs (SAEs). These should include cases of lack of compliance or patients who discontinue participation without returning the study medication.

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

Additionally, you should look for drug accountability discrepancies (e.g., missing medication, loss of drug, or non-compliance cases in which more investigational drug has been used compared to the expected use). Investigators should obtain more information and explanations from these subjects when there are instances of such drug accountability discrepancies.

For additional details regarding the documentation of AEs consult Section V.B. of the January 2017 CDER guidance for industry, *Assessment of Abuse Potential of Drugs*, available at,
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf.

Discussion
There was no further discussion of this question.

Question 18: *The Applicant plans to address the special populations (i.e. populations with hepatic or renal insufficiency) or drug-drug interactions assessment based on all information already identified for tramadol and celecoxib, and adopt their well-established recommendations on special populations and drug-drug interactions for NDA approval. Does the FDA agree?*

FDA Response:
You stated in the meeting package that the recommendations on special populations (i.e., populations with hepatic or renal insufficiency) (b) (4)

Your proposal (b) (4) **may not be acceptable** (b) (4)

We note that, since E-58425 is a fixed-dose combination product, it may be difficult to dose adjust in several situations. You need to clearly elaborate:

a. **How E-58425 will be initiated, e.g., using the Ultram label as an example, i.e., ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.**

b. **Dosing recommendations regarding special populations, e.g., hepatic, renal and elderly, etc.**

c. **Dosing recommendations regarding drug-interaction, e.g., poor metabolizers of CYP2C9, inhibitors of CYP2D6 and 3A4, inducers of CYP3A4, etc.**

The acceptability of your proposed dose adjustment plan will be a review issue after NDA submission.

Discussion

Regarding response 18a., the Sponsor provided a rationale as to why they consider that no titration is needed for initial dosing. The Division stated that, while titration is not required, the Sponsor should consider that many patients may not tolerate the initial dose.

Regarding response 18b., the Sponsor proposed (b) (4) The Agency stated that it is premature to agree on a final recommendation, which will be made pending review of the application. (b) (4)

(b) (4)
The Agency did not agree with the current proposal, (b) (4) The Sponsor must either provide adequate justification or an additional study to support their (b) (4) proposal, or employ conservative labeling based on the potential for differential systemic exposure in special populations. Further, in reference to the 505(b)(2) application pathway, if the Sponsor plans to rely on previous findings from additional listed drug(s), the Sponsor must patent certify any information used in the labeling, and consider appropriate BA studies to make sure there is a scientific bridge established.

Regarding response 18c., the Sponsor proposed (b) (4) The Agency stated that the Sponsor should use the same strategy described above.

Question 19: *The dosing regimen for Co-crystal E-58425 that has been tested in clinical studies is every twelve hours. The Applicant considers that with all the clinical and non-clinical information for Co-crystal E-58425 complemented with pharmacokinetic modeling data,* (b) (4) *can be supported in the label. Does the FDA agree?*

FDA Response:
We are open (b) (4) **you must provide sufficient clinical data** (b) (4) **will be reviewed, we anticipate additional clinical data will be needed to support the proposed dosing regimen.**

You indicate (b) (4) **In your submission, provide evidence** (b) (4) **the acceptability of the proposed** (b) (4) **will be a review issue.**

Discussion
The Sponsor stated (b) (4)

The Sponsor asked (b) (4)

(b) (4)

(b) (4)

Post Meeting Note:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Additional Nonclinical Comments

1. **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 ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and 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.**

2. **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.

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

and

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

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

3. 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.

4. We remind you that new excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry:

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

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

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

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

5. **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 approved products, 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.

6. **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 Module 2 of the NDA submission. Include copies of all referenced citations in the NDA submission in Module 4. Translate all journal articles that are not in English into English.**

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. **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.**

Discussion
There was no further discussion of these comments

3.0 GENERAL COMMENTS

PREA REQUIREMENTS

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

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/

UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SECURE EMAIL COMMUNICATIONS

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

ABUSE POTENTIAL ASSESSMENT

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

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

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

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

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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

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

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature

Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

Discussion
There was no further discussion of these additional comments.

4.0 ACTION ITEMS

1. The Division will provide a post-meeting note (b) (4) (b) (4)

2. The Division will provide input on the Sponsor's proposed study design and endpoints through either a Type C meeting or Written Responses, if the Sponsor submits a request and protocol.

5.0 ATTACHMENTS AND HANDOUTS

PDF Handout titled: Materials for the discussion at the pre-NDA meeting IND 128177. May 17, 2018

27 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

DIANA L WALKER
06/18/2018