CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212994Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 130463

MEETING MINUTES

KemPharm, Inc.
Attention: Marcus Juliano
Senior Director of Regulatory Affairs
1180 Celebration Blvd.
Suite 103
Celebration, FL 34747

Dear Mr. Juliano:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KP415/dexmethylphenidate hydrochloride.

We also refer to the meeting between representatives of your firm and the FDA on April 10, 2019. The purpose of the meeting was to obtain feedback on the acceptability of the nonclinical and clinical program for NDA submission, and to obtain feedback on the sufficiency of the drug abuse potential assessment program.

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 Keith Kiedrow, Team Leader, Senior Regulatory Project Manager at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

Tiffany Farchione, M.D.
Acting Director
Division of Psychiatry Products
Office of Drug Evaluation I

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:	April 10, 2019, 11AM-12NOON EST
Meeting Location:	FDA White Oak Building 21 Room 1537
Application Number:	130463
Product Name:	KP415/dexmethylphenidate hydrochloride
Indication:	ADHD
Sponsor/Applicant Name:	KemPharm, Inc.

FDA ATTENDEES

Tiffany R. Farchione, MD	Acting Director, Division of Psychiatry Products (DPP)
Javier A. Muñiz, MD	Associate Director for Therapeutic Review, DPP
Jasmine Gatti, MD	Clinical Team Leader, DPP
Greg Dubitsky, MD	Clinical Reviewer, DPP
Ikram Elayan, PhD	Pharmacology/Toxicology Supervisor, DPP
Antonia Dow, PhD	Pharmacology/Toxicology Reviewer, DPP
David Claffey, PhD	Office of Pharmaceutical Quality (OPQ)
Peiling Yang, PhD	Biometrics Team Leader, Division of Biometrics I (DBI)
Thomas Birkner, PhD	Biometrics Reviewer, DBI
Luning Zhuang, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Praveen Balimane, PhD	Clinical Pharmacology Reviewer, OCP
Shalini Bansil, MD	Reviewer, Controlled Substance Staff (CSS)
Keith Kiedrow, PharmD	Team Leader, Senior Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Travis Mickle, PhD	CEO
Sven Guenther, PhD	Executive Vice President, Research and Development
Christal Mickle, MA	Vice President, Product Development
Andrew Barrett, PhD	Vice President, Scientific Affairs
Rene Braeckman, PhD	Vice President, Clinical Development
Christopher Lauderback, PhD	Vice President, Manufacturing
Adam Smith, PhD	Senior Director, Research
Marcus Juliano	Senior Director, Regulatory Affairs

1.0 BACKGROUND

KemPharm, Inc. has developed a prodrug of dexmethylphenidate (d-MPH) called KP415 (or

serdexmethylpenidate) for the treatment of attention deficit hyperactivity disorder (ADHD). KP415 alone was intended to provide a therapeutic effect over an extended period each day by controlled production of d-MPH over time. Because of a delay in the production of d-MPH after administration of KP415 alone (a Tmax of about 8 hours), the Sponsor has co-formulated KP415 with immediate-release d-MPH, which is intended to provide therapeutic blood levels of d-MPH during the first several hours after administration.[1]

The Sponsor plans to submit a 505(b)(2) NDA for the combination formulation (KP415/d-MPH) that will reference safety and efficacy findings for Focalin XR, an approved extended-release formulation of dexmethylphenidate, as the Listed Drug (LD).

The Division provided feedback on this development program on several occasions:

- Pre-IND Written Response Only (WRO) comments dated July 1, 2016, provided advice on nonclinical studies to more completely elucidate the pharmacokinetic (PK) profile of KP415, the design of the initial phase 1 study to evaluate the oral bioavailability of KP415 relative to a methylphenidate comparator, and the 505(b)(2) pathway to approval. Also, the Controlled Substances Staff (CSS) advised the Sponsor that the abuse potential of KP415 alone must be evaluated because it is not currently scheduled as a controlled substance.

- A September 6, 2016, request for Fast Track designation was denied because the Sponsor did not demonstrate that an unmet medical need existed. A second request for Fast Track designation on May 15, 2018, was denied for the same reason.

- An End-of-Phase 1 meeting was held on June 14, 2017. The Division advised the Sponsor that additional animal studies may be needed to qualify KP415 alone and any other major human metabolites. The need for such studies will depend on identification of the *in vivo* human metabolic profile and concentrations of circulating entities at steady state. Other discussion topics included the potential need to conduct additional PK studies (e.g., in subjects with renal and hepatic impairment and drug-drug interaction studies), the design of a PK bridging study, the need for further information before reaching agreement on extrapolation of efficacy from children to adolescents, the design of a pivotal efficacy trial in children (including the choice of the time point as the baseline value for the primary efficacy endpoint, which became the topic of WRO comments dated October 10, 2018), and studies to evaluate human abuse potential (HAP) (including *in vitro* tampering studies).[2]

- An End-of-Phase 2 meeting was held on November 14, 2017. The Division indicated that KP415 alone is a new molecular entity (NME) that is not rapidly metabolized to d-MPH. Based on human PK data at steady state, KP415 alone accounted for up to 27% of total drug-related circulating material at Cmax and up to 13% of total drug-related material for AUC_{0-24},

[1] Consistent with previous submissions under this IND, KP415 refers to the prodrug alone and KP415/d-MPH refers to the combination formulation.
[2] The discussion of the pivotal efficacy trial included the choice of the time point for the baseline value for the primary efficacy analysis. This issue became the topic of WRO comments dated October 10, 2018.

both based on molar concentrations. These fractions exceed the (b) (4)% threshold for qualification and, therefore, the Division stated that KP415 itself required adequate assessment for toxicity in animals. The Division would accept a single juvenile animal study in lieu of a chronic toxicity study and a juvenile animal study if the dosing duration in the juvenile study is extended to cover chronic use in humans. Other issues that were discussed included the need to meet ICH E1 exposure requirements to adequately assess long-term clinical safety, the need to compare PK data across child, adolescent, and adult age ranges to support safety and efficacy in patients age 6 years and older, feedback from CSS on proposed HAP studies, and the need to evaluate the potential for alcohol-induced dose dumping.

- The Division agreed with an amended initial Pediatric Study Plan (iPSP) on August 2, 2018. The iPSP provided for a 6-month juvenile rabbit toxicity and toxicokinetic (TK) study, development of an age-appropriate formulation for children ages 4 to less than 6 years, a waiver of PREA requirements for children under age 4, a deferral for an open label PK and safety study in children ages 4 to less than 6 years, and a safety and efficacy study in children ages 6 to less than 13 years.

- WRO comments dated October 10, 2018, addressed concerns regarding the protocol-specified analysis of data supporting therapeutic onset and duration of effect claims from the pivotal efficacy study (Study KP415.E01). The baseline time point specified in the protocol (first day of randomized treatment) differed from that usually implemented in similar laboratory classroom studies (the day of the laboratory classroom study) and yielded results which the Sponsor felt did not reflect the true magnitude of onset and duration of therapeutic effect. A post-hoc analysis was claimed to be more accurate. The Division advised the Sponsor to discuss this issue in the NDA. The Division's decision on the acceptability of the post-hoc analysis will be a matter for review.

- WRO comments dated January 28, 2019, addressed Sponsor questions pertaining to the filing and format issues of the Chemistry, Manufacturing, and Controls (CMC) module of the planned NDA submission.

The nonclinical development program includes CNS, respiratory, and cardiovascular safety studies; a hERG safety assay; animal ADME, TK, mass balance, and CYP inhibition and induction studies; 28-day rat and dog toxicity studies; a 6-month juvenile rabbit study; genotoxicity studies; and a reproductive toxicity study. Important clinical studies are shown in Table 1.

Table 1: Important Clinical Studies

Study ID	Study Description
Phase 1 Studies	
Study KP415.109	Comparative PK study with Concerta in healthy adults to identify the optimal ratio of KP415 and d-MPH for the combination product.
Study KP415.104	PK food effect study of KP415/d-MPH capsules in healthy adults.
Study KP415.105	Single-dose PK study of KP415 alone in children and adolescents with ADHD.

Study KP415.107	PK bridging study comparing KP415/d-MPH capsules with Focalin XR in healthy adults.
Study KP415.110	Dose proportionality and steady state PK study of KP415/d-MPH in healthy adults.
Phase 3 Studies	
Study KP415.E01	Pivotal safety and efficacy study of KP415/d-MPH in children (ages 6 to 12 years) with ADHD.
Study KP415.S01	Ongoing, 12-month open label safety study in children with ADHD (ages 6 to 12 years at the start of study drug treatment).

Approximately 782 unique subjects will have received at least one dose of KP415 (alone or combined with d-MPH) in clinical studies at the time of NDA submission. Of these, 426 will have received multiple doses of KP415/d-MPH, with 189 patients treated for at least 6 months and 100 patients for 12 months.

The objectives of this pre-NDA meeting are to discuss the following:

1. Acceptability of the overall nonclinical program for filing.
2. Acceptability of the proposed clinical package (PK, efficacy, and safety) for filing.
3. Adequacy of the drug abuse potential assessment program.

FDA sent Preliminary Comments to KemPharm, Inc. on April 8, 2019.

2. DISCUSSION

1.1 NONCLINCIAL QUESTIONS

Question 1: KemPharm believes that the completed nonclinical studies summarized in section **Error! Reference source not found.** are sufficient to support acceptance of the NDA for filing, and that no further studies are necessary for the Division's review of the nonclinical portion of the NDA. Does the Division agree?

FDA Response to Question 1: *We are unable to answer this question. This will be a matter for review after you submit the study reports for the 6-month study in juvenile rabbits and the embryo-fetal development study in rabbits. We need to evaluate the data to ensure that there are no findings of toxicity that could be attributed to the prodrug or anything else other than methylphenidate.*

Discussion: *No further discussion.*

1.2 CLINICAL QUESTIONS

Question 2: Does the Division agree that the clinical package presented in section **Error! Reference source not found.** is adequate to support filing an NDA for the proposed indication, and that no other studies are needed?

FDA Response to Question 2: *No, we disagree. Because KP415 is an NME, you should perform a comprehensive clinical pharmacology characterization of KP415 to support the filing of a NDA. Some additional studies required for KP415 are listed below (not an exhaustive list):*

- *PK studies in subjects with renal or hepatic impairment.*
- *A thorough QT study. If you feel that a waiver of the requirement for a TQT study is justified, you may submit a formal waiver request for review by our QT Interdisciplinary Review Team (QT IRT).*
- *Complete characterization of drug-drug interaction potential of KP415 (via in vitro and clinical studies) as per the recent guidance's by the agency (available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm). These studies are required for the prodrug (KP415) as well as major circulating metabolites (e.g., ritalinic acid).*

Study reports for the above investigations must be included in your NDA submission or your application will not be filed.

Additionally, we have the following comments:

- *Please confirm that the final "to-be-marketed" formulation was used in the pivotal efficacy/safety studies as well as the key clinical pharmacology studies (i.e., the PK bridging study, food-effect study, drug interactions study, and the dose proportionality study)*
- *Please confirm that the food-effect study was conducted using the final "to-be-marketed" formulation using the highest strength or the highest therapeutic dose.*
- *We recommend the content and format of information found in the Clinical Pharmacology sections (Section 7, 12, etc.) of labeling submitted to support this application be consistent with FDA Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.*

Sponsor responses to preliminary comments for Question 2:

- PK studies in subjects with renal or hepatic impairment
    - KemPharm's current clinical and nonclinical data do not indicate that renal and hepatic studies in subjects with compromised organ function are warranted. Study KP415.111

demonstrated that <1% of SDX is excreted renally, and thus the kidney is not a major route of elimination for SDX. Additionally, data from liver S9 fractions and in vitro drug-drug interaction panels indicate that SDX is not metabolized in the liver, nor is it an inhibitor, inducer, or substrate of any CYP enzymes. There were also no new major metabolites found in systemic circulation. As such, would it be appropriate to submit the NDA with these full supporting data and the associated justification and would the Division accept this for filing of the NDA without these clinical studies?

- A thorough QT study

  - KemPharm has conducted a number of nonclinical studies relevant for assessing any effects on QT interval, including a cardiovascular safety pharmacology study, a hERG safety assay, and 14- and 28-day repeat dose toxicology studies in telemeterized dogs. Additionally, all of the clinical pharmacology studies have examined QT interval at time intervals corresponding to the T_{max} of the treatment (SDX alone or SDX/d-MPH capsules). There have not been any clinically significant findings in any of the nonclinical or clinical studies. KemPharm plans to submit a waiver for the requirement for a TQT study. Does the Division suggest that KemPharm submit the waiver prior to the NDA or along with NDA?

- Complete characterization of drug-drug interaction potential of SDX

  - KemPharm's current nonclinical data have not met the threshold required to perform clinical DDI studies and do not indicate that clinical DDI studies are warranted. KemPharm has tested the in vitro DDI potential of SDX according to the guidance for "In Vitro Metabolism and Transporter Mediated DDI Studies", and the NDA will include the required in vitro studies according to this guidance. Is it acceptable to the submit the NDA with the complete set of in vitro DDI testing conducted on SDX as per the aforementioned guidance and the associated justification and would the Division accept this for filing the NDA without any clinical DDI studies?

  - No testing was performed for ritalinic acid since it is the major metabolite of MPH in all approved MPH products, including our RLD, Focalin XR. Does the Division agree?

  - KemPharm confirms that all pivotal clinical studies, including the PK bridging study, food effect study, and dose-proportionality study, were conducted with the final, to-be-marketed capsules. The food effect study was conducted with the highest strength capsule which is also the highest, daily therapeutic dose.

Discussion: *The Agency reiterated the need for organ impairment studies (renal and hepatic impaired) keeping in mind the high levels of SDX (prodrug) in circulation at steady state. We are concerned that SDX is a novel, un-approved moiety and will be present in high levels in circulation for a chronically administered drug and could accumulate in patients with organ impairment. However, the Sponsor clarified that they have significant amount of additional preclinical and clinical data and supporting evidence that supports their request for waiver of the organ impaired studies. We requested that the Sponsor provide a comprehensive*

justification for the waiver for both the hepatic impaired and renal impaired study. They will provide their exhaustive rationale including but not limited to concrete data from in vitro, pre-clinical, and clinical studies and the associated justifications to support the waiver. The acceptability of the waiver will be a matter of review following submission of the requested information.

Regarding the need for additional drug-interaction studies, the Agency reminded the Sponsor to perform the comprehensive panel of studies (as recommended by the Guidance) for all major circulating moieties (SDX, any intermediates, etc.). Justification will also be provided that ritalinic acid is not formed directly by-passing the MPH formation.

The Sponsor confirmed that all pivotal clinical studies, including the PK bridging study, food effect study, and dose-proportionality study, were conducted with the final, to-be-marketed capsules.

The Sponsor plans to request a waiver of the requirement for a thorough QT study. The Division advised the Sponsor to submit this request as soon as possible to allow the Division sufficient time to consult with the QT Interdisciplinary Review Team prior to NDA submission. The Division advised that the request should include a detailed description of ECG data collection from their phase 1 studies or other supporting studies, ECG parameters at Tmax for KP415, and ECG data at supratherapeutic blood levels in humans, which the Sponsor intended to address using data from the intravenous administration of KP415 alone in their human abuse liability study.

Given the absence of data directly comparing immediate release (IR) d-MPH to KP415 alone, the Division questioned the contribution of KP415 alone to the observed plasma levels of d-MPH and clinical efficacy of the product, raising the possibility that most of the active moiety is derived from the IR component of the product. The Sponsor stated that KP415 alone does generate delayed and prolonged-release d-MPH to provide efficacy later in the day after d-MPH levels from the IR component have declined. They indicated that this is supported by PK modeling comparing KP415 with IR d-MPH. In addition, there is extensive published literature on the PK of IR d-MPH for comparison with KP415 alone.

Assuming that efficacy may last for 12 or 13 hours after dosing, the Division emphasized the importance of evaluating adverse events, such as insomnia, that may occur late in the day.

Question 3: Does the Division agree that the efficacy data from Phase 3 study KP415.E01 (summarized in section **Error! Reference source not found.**) are adequate to assess the efficacy of SDX/d-MPH for the proposed indication? APPEARS THIS WAY ON ORIGINAL

FDA Response to Question 3: *Study KP415.E01 appears to be adequate to assess the efficacy of KP415/d-MPH in the treatment of ADHD in children ages 6 to 12 years.*

Sponsor responses to preliminary comments for Question 3: Thank you for your response regarding Study KP415.E01. KemPharm would appreciate clarification regarding the WRO

comments that were received on October 10th, 2018 regarding the post-hoc analyses. Given the justification originally submitted, does the Agency agree that writing a similar justification in the NDA to use the post-hoc analyses to determine onset and duration is acceptable?

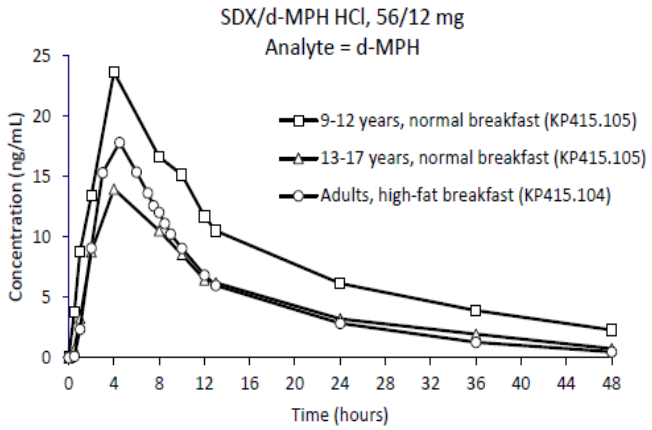
Discussion: *The October 2018 justification for the post hoc analysis appears reasonable but the acceptability of this analysis* (b) (4) *will be a matter for review. The Division noted that, in the post hoc analysis, the mean changes from baseline in the SKAMP-C at 12 and 13 hours post-dose indicate worsening ADHD symptoms in the KP415/d-MPH-treated patients compared baseline, although the changes were statistically superior to those in placebo-treated patients. Thus,* (b) (4) (b) (4) *these findings should be addressed in their application. The Sponsor stated that one possible reason is fatigue at the end of the laboratory classroom day. They agreed to address these findings in their NDA.*

Question 4: Based on the results of the dose-proportionality PK study (KP415.110 summarized in **Error! Reference source not found.**) in adults and the PK bridging study in children and adolescents (KP415.105 summarized in section **Error! Reference source not found.**), does the Division agree with the justification provided in the briefing package that efficacy findings in children 6-12 years of age from the KP415.E01 study can be used to support efficacy in all patients ≥ 6 years of age?

APPEARS THIS WAY ON ORIGINAL

FDA Response to Question 4: *The extrapolation of efficacy from children (ages 6 to 12 years) to adolescents (ages 13 to 17 years) and to adults (18 years and older) will be a matter for review. You have provided a comparison of PK data from children (ages 9 to 12 years), adolescents (ages 13 to 17 years), and adults, all under fed conditions (see Figure 1 below from page 110 of the briefing document). You claim that bridging to adolescents and adults is justified based on similarity of the shape of the PK profiles, your observation that normalization for body weight produces CL/F values that are comparable across age ranges, and the fact that optimal dosing is determined by titration in clinical practice. We request that your application also provide the rationale for identification of appropriate doses for adolescents and adults in view of the observation that PK is weight-dependent.*

Figure 1: Plasma Concentration-Time Profiles for d-MPH Following Administration of KP415/d-MPH (56 mg/12 mg)



-

Discussion: *The Division reiterated that because PK appears to differ by age group, the NDA should provide the rationale for dosing in each age group to support instructions in the Dosage and Administration section of labeling. The Division noted that marketed products often have specific dosing instructions for different age groups. The Division also cautioned that although efficacy may be extrapolated across age groups, safety may not because, for example, the safety profile in children may be different from that in older adults despite similar PK. Thus, safety should be addressed for each age group. The Sponsor responded that stimulant dosing in patients with ADHD is generally done by titration to clinical response. They agreed to address these concerns in their application.*

APPEARS THIS WAY ON ORIGINAL

Question 5: Does the Division agree that the food effect PK data (KP415.104 summarized in **Error! Reference source not found.**) are sufficient to state that SDX/d-MPH can be taken with or without food in the (b) (4) Dosage and Administration sections of the Label?

FDA Response to Question 5: *The exact label language will be a review issue.*

Discussion: *No further discussion.*

APPEARS THIS WAY ON ORIGINAL

Question 6: Based on the totality of the nonclinical package, clinical findings with associated safety database, and reliance on RLD Focalin XR to support safety of SDX/d-MPH, KemPharm plans to submit the NDA with 6-months safety data from the KP415.S01 study (summarized in section **Error! Reference source not found.**) to satisfy the long-term exposure requirements. When compared to d-methylphenidate, no additional safety concerns have been identified throughout the development program for this drug product. Does the Division agree with this approach?

FDA Response to Question 6: *We agree that safety data from subjects who have completed at least six months of continuous treatment in Study KP415.S01 is acceptable for filing the application for purposes of long-term safety exposure. However, the 120-Day Safety Update Report should contain safety data from a cumulative exposure that meets ICH E1 recommendations for an NME (i.e., at least 300 patients exposed for at least six months and 100 patients for at least 12 months at dosage levels intended for clinical use).*

Discussion: *No further discussion.*

1.3 Abuse Potential Questions

Question 7: Does the Agency agree that the abuse potential package summarized in section **Error! Reference source not found.**, including completed human abuse potential studies and ongoing in vitro tampering assessment, provide data sufficient to inform a scheduling decision under the Controlled Substances Act for SDX?

FDA Response to Question 7: *Yes; these studies will assist in formulating a scheduling decision for SDX under the Controlled Substances Act. However, a scheduling decision will also be based on abuse-related adverse events (AE) occurring in all clinical studies.*

You should document 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.

Sponsor responses to preliminary comments for Questions 7, 8, and 9: To clarify questions 7, 8 and 9, KemPharm agrees that the drug product SDX/d-MPH will be schedule II. KemPharm plans to submit documentation for abuse-related AEs for the final drug product. In addition, for SDX alone, which is not currently scheduled, we will submit clinical abuse liability studies, abuse-related AE documentation, in vitro tampering studies, and other relevant data to support scheduling of the currently unscheduled prodrug. Does the Agency agree with this approach?

Discussion*: The Sponsor was advised that their question regarding scheduling SDX alone will be answered in post-meeting comments after internal discussion.*

Post-Meeting Comment
Yes; we agree with this approach. The Agency will make scheduling recommendations to the DEA for SDX alone under this NDA.

Your NDA submission should provide abuse-related information and cross-linkage in appropriate sections of the NDA, as follows:

1. *Section 1.11.4 should contain your proposal and rationale for placing or not placing SDX into any schedule of the CSA.*

2. *Section 2.7.4 should contain a subsection devoted to details of your abuse potential assessment, including a description of data, interpretation, and discussion of all abuse potential data provided in the NDA under other modules, including any drug accountability discrepancies and an analysis of abuse-related adverse events.*

   Section 2.7.4 should also contain a comprehensive table of contents that provides links to all studies (nonclinical and clinical) and references in the NDA submission related to the assessment of abuse potential.

Question 8: Based on comments received from the EoP1 and EoP2 Meetings, KemPharm has conducted the required human abuse potential studies of SDX (administered orally, intranasally, and intravenously) to help inform a scheduling decision under the Controlled Substances Act. Does the Division agree that data from these studies can be included in the label?

FDA Response to Question 8: *Inclusion of these studies in the label will be a review issue. We remind you that KP415/d-MPH capsules will be placed under Schedule II of the Controlled Substances Act because they contain MPH, a Schedule II substance*

Discussion: *See discussion under Question 7.*

Question 9: KemPharm provided in vitro tampering protocols in a CMC amendment to IND 130463 on 7/24/2018 under Serial No. 0044/eCTD sequence 0045. These protocols were related to the abuse potential assessment of the drug substances in SDX/d-MPH capsules as well as the drug product itself and Division comments were requested on the overall study design of these assessments. These assessments are summarized in section **Error! Reference source not found.**. Does the Division have any comments on the protocols submitted to the IND on 7/24/2018 or the overall study design presented in these briefing materials?

FDA Response to Question 9: *The Agency does not have any specific comments on the in vitro tampering protocols. The data from the studies may provide general chemical understanding of the chemistry and stability of the prodrug and the drug product.*

Although planned studies focused on the conversion of the prodrug to d-methylphenidate, it is unclear how the proposed drug product could have less abuse potential than Focalin or Focalin XR. The proposed product contains more d-methylphenidate hydrochloride (12 mg) than the highest strength Focalin tablet (10 mg) and, given that the proposed product is already formulated as a powder, it will ease abuse by the intranasal route. The highest strength Focalin XR capsule does contain more immediate release d-methylphenidate (20 mg) at its highest

strength than the proposed product (12 mg). However, Focalin XR's drug is bound to sugar spheres whereas the proposed product contains unbound drug which appears to be more readily abusable by the intranasal route.

Discussion: *See discussion under Question 7.*

1.4 NDA Content and General Filing Strategy

Question 10: A proposed Table of Contents for the NDA is provided in **Error! Reference source not found.**. Does the Division agree that this represents, on face, the contents of a complete application that is sufficient for filing?

APPEARS THIS WAY ON ORIGINAL

FDA Response to Question 10: *We have the following comments on the Table of Contents provided in Appendix 1:*

- *All labeling in Section 1.14 must comply with the requirements of the Physician Labeling Rule (PLR), including the Pregnancy and Lactation Labeling Rule (PLLR), as described in 21 CFR 201.57.*
- *The efficacy claim indicated for Section 2.7.3* (b) (4) (b) (4) *should read "Treatment of Attention Deficit Hyperactivity Disorder."*
- *Section 2.7.3 must contain a description of the benefit-risk assessment for your product.*

Discussion: *No further discussion.*

Question 11: Given that a single Phase 3 study KP415.E01 provides the primary efficacy data to support SDX/d-MPH for the proposed indication, with additional supportive efficacy data from long term safety study KP415.S01, KemPharm does not plan to prepare and submit a separate Integrated Summary of Efficacy in Module 5. Instead, efficacy data and analyses presented in the integrated summary of efficacy will be generated from the E01 and S01 individual study-level databases, and will be appropriately summarized in Module 2.7.3 Summary of Clinical Efficacy. Does the Division agree with this approach?

FDA Response to Question 11: *Yes, we agree that no ISE is required.*

Sponsor responses to preliminary comments for Question 11: The primary safety data for SDX/d-MPH for the proposed indication are from Studies KP415.E01, KP415.S01, KP415.105, KP415.107, KP415.109, KP415.110, KP415.101, KP415.102, KP415.104, KP415.106, KP415.108, and KP415.111. KemPharm proposes to submit the text for the Integrated Summary of Safety in Module 2.7.4, with any large appendices and datasets placed in Module 5.3.5.3. Does the Agency agree with this approach?

Discussion: *The Division confirmed that a summary of safety data from all studies may be presented in Module 2.7.4, with large appendices and datasets in Module 5.3.5.3, in lieu of an Integrated Summary of Safety in Module 5.*

Question 12: Per 21 CFR 314.50(f)(2), KemPharm will only submit case report forms for each patient in the Phase 2 and Phase 3 studies who discontinued due to an adverse event, as well as CRFs for patients who experienced serious adverse events. Does the Division agree with this proposal?

FDA Response to Question 12: *We agree and additionally request case report forms for any phase 1 study subject who experienced a serious adverse event or discontinued treatment due to an adverse event. Also, we request that narrative summaries be provided for all patients for whom a case report form will be submitted.*

Discussion: *No further discussion.*

Question 13: Does the Division agree that no risk evaluation and mitigation strategy (REMS) or any other REMS elements beyond the medication guide are required for the SDX/d-MPH NDA submission? Also, does the Division anticipate the need for any non-REMS risk management plans to the included in the NDA?

FDA Response to Question 13: *We do not anticipate the need for a REMS or any non-REMS risk management plan as part of the NDA submission at this time. The need for these measures will be a matter for review during our examination of your application.*

Discussion: *No further discussion.*

Question 14: Program code used to create the analysis datasets, tables, listings, and figures in the Phase 3 KP415.E01 and KP415.S01 studies will be submitted. All code will be submitted as ASCII text files and will include supporting documentation. Does the Division agree with the proposed programming code submission strategy for the Phase 3 KP415.E01 and KP415.S01 studies?

FDA Response to Question 14: *Assuming that you will submit SAS code in the text file format mentioned, we agree.*

Please include the following items for the phase 3 studies in your NDA submission:

- *All raw and derived variables; if clinical data were not originally collected in SDTM format, you would need to submit raw data in the legacy format, as well as the detailed descriptions of mappings from the legacy to the SDTM format together with a document of variables definition;*

- *The SAS programs that produced all efficacy results (intended for labeling description);*
- *The SAS programs by which the derived variables were produced from the raw variables;*
- *A list of IND number with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*

Discussion: *No further discussion.*

Question 15: The safety of SDX/d-MPH will primarily be evaluated using data from the phase 3 studies KP415.E01 and KP415.S01. KemPharm will also provide limited safety analyses from all phase 1 studies to address targeted safety questions. The SDX/d-MPH NDA will include integrated safety data for disposition (ADSL), demographics (ADSL), duration of exposure (ADSL), and adverse events (ADAE) from 12 studies: KP415.E01, KP415.S01, KP415.105, KP415.107, KP415.109, KP415.110, KP415.101, KP415.102, KP415.104, KP415.106, KP415.108, and KP415.111. Other safety data and analyses presented in the integrated summary of safety will be generated from the KP415.E01 and KP415.S01 individual study-level databases. Does the Agency agree with the plan for integrating safety data?

FDA Response to Question 15: *No, we do not agree. Except for purposes of tabulating numbers of patients exposed to drug and duration of exposure, these 12 studies should not be pooled. We will review safety and efficacy data on a study-by-study.*

Discussion: *No further discussion.*

Question 16: The pooled safety analysis pooling groups planned for the integrated summary of clinical safety are listed under c, d and e below. Some of the studies listed below will also be analyzed individually for other specific safety evaluations. Does the Agency agree with the plan for pooling safety data in support of the NDA?

a. KP415.E01 classroom efficacy study
b. KP415.S01 long-term safety study
c. Studies Evaluating SDX/d-MPH in Children and Adolescents with ADHD (demographics, disposition, and exposure only): KP415.105, KP415.E01, and KP415.S01
d. Studies Evaluating SDX/d-MPH in Healthy Volunteers (demographics, disposition, and exposure only): KP415.104, KP415.107, KP415.109, and KP415.110
e. Studies Evaluating SDX in Healthy Volunteers (demographics, disposition, and exposure only): KP415.101, KP415.102, KP415.106, KP415.108, and KP415.111

FDA Response to Question 16: *No, please see our response to Question 15.*

Discussion: *No further discussion.*

Question 17: A Study Data Standardization Plan (SDSP) is provided with the Pre-NDA Briefing Materials which specifies the study data standards to be included in Modules 4 and 5 in the NDA submission. Does the Division agree with this proposed electronic data submission plan regarding database format (SDTM/ADaM) for the individual study databases that will be included in the NDA?

FDA Response to Question 17: *Yes, electronic datasets should be in SDTM/ADaM format.*

Discussion: *No further discussion.*

Question 18: To facilitate the pooling and interpretation of safety data, adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and provided in the integrated datasets. The medical history terms and medications will not be re-coded since no relevant impact on results interpretation is expected. Does the Division agree with this proposed MedDRA standardized coding plan?

FDA Response to Question 18: *Yes, this coding plan is acceptable. You should use the latest version of MeDRA for adverse event coding.*

Discussion: *No further discussion.*

Additional Comment
The Division prefers the Sponsor refer to and adhere to all guidance in the following resources:

https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

The Sponsor should refer to and adhere to the specific guidance provided in the following resource for collecting and submitting study data and programs:

https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624939.pdf

Discussion: *No further discussion.*

3.0 OTHER

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan, as well as a timeline for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential, and it was concluded that a REMS is not anticipated to be needed and it was agreed that the product will be Schedule II.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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.

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.

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.

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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIFFANY R FARCHIONE
05/10/2019 04:40:06 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 130463

MEETING MINUTES

KemPharm, Inc.
Attention: Marcus Juliano
Senior Director, Regulatory Affairs
1180 Celebration Blvd.
Suite 103
Celebration, FL 34747

Dear Mr. Juliano:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KP415.

We also refer to the meeting between representatives of your firm and the FDA on November 14, 2017. The purpose of the meeting was to discuss development plans for KP415.

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, email Ann Sohn, Regulatory Project Manager at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
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: End of Phase 2

Meeting Date and Time: November 14, 2017 at 12pm to 1pm
Meeting Location: 10903 New Hampshire Avenue, Bldg 22, Rm 1419
Silver Spring, MD 20903

Application Number: IND 130463
Product Name: KP415
Indication: ADHD
Sponsor/Applicant Name: KemPharm, Inc.

FDA ATTENDEES

Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Gregory Dubitksy, MD	Clinical Team Lead, DPP
Graciela Gonzalez, MD	Clinical Reviewer, DPP
Ikram Elayan, PhD	Pharmacology/Toxicology Supervisor, DPP
Antonia Dow, PhD	Pharmacology/Toxicology Reviewer, DPP
David Claffey, PhD	Chemistry Manufacturing and Controls (CMC) Lead for Psychiatry, Office of New Drug Products (ONDP)
Wendy Wilson-Lee, PhD	Acting Branch Chief, ONDP
Parnali Chatterjee , PhD	Biopharmaceutics Reviewer
Hao Zhu, PhD	Team Lead, Office of Clinical Pharmacology (OCP)
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Statistical Team Lead, Division of Biometrics I
Yang Wang, PhD	Statistical Reviewer, Division of Biometrics I
Shalini Bansil, MD	Reviewer, Controlled Substance Staff (CSS)
Ling Chen, PhD	Expert Mathematical Statistician, CSS
Ann Sohn, PharmD	Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Travis Mickle, PhD	President and Chief Executive Officer
Christal Mickle, MA	Vice President, Product Development
Sven Guenther, PhD	Executive Vice President, Research and Development
Rene Braeckman, PhD	Vice President, Clinical Development
Christopher Lauderback, PhD	Vice President, Manufacturing
Andrew Barrett, PhD	Sr. Director, Scientific Affairs

Marcus Juliano	Sr. Director, Regulatory Affairs
Adam Smith, PhD	Associate Director, Preclinical Science
Corinna Wetzel, PhD	Director, Product Development
(b) (4)	Toxicology Consultant

1.0 BACKGROUND

KemPharm intends to develop a combination of KP415 (a prodrug of d-threo-methylphenidate) and dexmethylphenidate (d-MPH) as a once-daily, extended release, abuse-deterrent product for the treatment of attention deficit-hyperactivity disorder (ADHD) in patients age 6 years and older.

The Sponsor plans to use the 505(b)(2) pathway to approval, referencing Focalin XR (dexmethylphenidate hydrochloride extended-release) capsules. Focalin XR is indicated for the treatment of ADHD in patients age 6 years and older. Focalin XR is administered once daily with a maximum dose of 30 mg/day in pediatric patients and 40 mg/day in adults.

The Sponsor co-formulated KP415 with a fixed dose of immediate-release (IR) d-MPH to provide adequate exposure to d-MPH in the first several hours post-dose, after which sustained d-MPH exposure will be provided primarily by KP415 conversion to d-MPH.

Four Phase 1 studies with the prodrug alone have been completed. An additional completed Phase 1 study (KP415.109) involved co-administration of the prodrug with d-MPH to evaluate the comparative pharmacokinetics (PK) of different ratios of d-MPH and the prodrug to identify the optimal ratio of d-MPH to KP415.

Five additional PK studies with the drug combination are planned, including a study of PK in children (6 to 12 years old) and adolescents (13 to 17 years old) and a PK bridging study to Focalin XR in adults. Also, a placebo-controlled efficacy study and an open-label 3-month safety study in children with ADHD will be conducted to demonstrate safety and efficacy.

The efficacy trial (KP415.E01) will be a multicenter, dose-optimized, double-blind, randomized, placebo-controlled, parallel efficacy laboratory classroom study in 176 children (6 to 12 years old) with ADHD. Study treatment will consist of a 21-day Dose Optimization Phase and a 7-day Treatment Phase with efficacy assessed on the final day in a laboratory classroom. The SKAMP will be administered at pre-dose and at 0.5, 1, 2, 4, 8, 10, 12 and 13 hours post-dose on the laboratory classroom day. The primary efficacy endpoint will be the average of the change from baseline in the SKAMP-C score collected across the laboratory classroom day.

In addition, the Sponsor is currently conducting an intravenous human abuse potential study and plans to conduct an oral human abuse potential study and an intranasal human abuse potential study with KP415.

The Sponsor's stated objective for this meeting is to discuss the following:

- Appropriateness of their clinical development strategy for KP415
- Appropriateness of their nonclinical package for KP415

- CMC development plans for KP415 drug substance and KP415 drug product
- Assessment of abuse potential of KP415

2.0 QUESTIONS AND RESPONSES

2.1 NONCLINICAL

Question 1: Does the agency agree with the general design of the juvenile rat toxicity study (Section 7.4.1)?

FDA Response to Question 1: *No, we do not agree with the general design of the juvenile rat toxicity study. See FDA Response to Question 3 for details.*

Discussion: *No further discussion.*

Question 2: Does the agency agree with the general design of the Embryo Fetal Development (Seg II) study (Section 7.4.2)?

FDA Response to Question 2: *We do not generally provide feedback on study design for Embryo Fetal Development Studies. We refer you to Guideline for Industry Detection of Toxicity to Reproduction for Medicinal Products (ICH-S5A) for Agency guidance. However, we note that the proposed species for this study is rat. If only one embryo fetal development study is determined to be needed for this development program, you will need to provide justification for the species choice. See FDA Response to Question 3 for details.*

Discussion: *No further discussion.*

Question 3: Based on studies summarized in Section 7.4 and completed studies summarized in Section 7.3, KemPharm believes this constitutes a full nonclinical program sufficient for NDA filing (see Discussion in Section 7.5), assuming no safety concerns are identified. Does the Agency agree?

FDA Response to Question 3: *No, we do not agree that the completed nonclinical studies and the proposed nonclinical studies constitute a full nonclinical program sufficient for NDA filing. KP415 is an NME that is not rapidly metabolized to d-MPH and that will be used chronically; therefore, KP415 needs to be adequately assessed for toxicity.*

Although we stated in the May Proceed letter (dated November 2, 2016) that if human PK data showed that exposures to KP415 were less than (b)(4) *% of the total drug-related material you might only need a bridging study of 28 days in animals, this* (b)(4) *% threshold was based on KP415 alone and not in combination with d-MPH. As Post Meeting Comments to Meeting Minutes dated July 14, 2017, we stated that based on the human PK data submitted at that time we believed it is not appropriate to base the need for additional animal studies on the percentage of the levels of the*

prodrug to the total drug-related material and that the approximately 5-hour half-life of KP415 was concerning to us, but the need for additional animal studies would be dependent on human PK data at steady state. Although you have submitted clinical PK data at steady state, this data is for the combination of KP415 with d-MPH and not KP415 alone.

In addition, we note that your d-MPH:KP415 ratios and percentage circulating calculations are based on molarity (nmol/L) rather than weight (ng/mL). However, this is not appropriate because KP415 is a prodrug of d-MPH and has a molecular weight approximately double d-MPH so you are artificially showing a bigger difference in exposures of KP415 to d-MPH after repeated dosing than exists if the data were to be assessed based on weight. When repeat-dose human data is assessed based on weight, even in combination with d-MPH, KP415 is present at similar exposures to d-MPH in humans. Based on your summary of human clinical exposures for single dose 20 mg, 40 mg, and 60 mg KP415 (page 58) you state that KP415 accounts for up to 27% of total circulating material at Cmax and up to 13% of total drug-related material for AUC0-24 hr, which is above the (b) (4)% threshold, and that d-MPH exposures are less than KP415 exposures when compared on a molar basis. When comparisons are made based on weight, KP415 exposures will be present at a greater percentage of total circulating material.

Therefore, KP415 will need to be adequately assessed for toxicity in animals. Because KP415 will potentially be used chronically, a chronic toxicology study in one species would be needed in addition to the proposed juvenile animal study. However, we would accept a juvenile animal study in lieu of two studies (chronic study and juvenile animal study), if the dosing duration of the juvenile study is extended to cover chronic use in humans. Because there are substantial species differences in PK, you will need to provide justification for species choice for this chronic juvenile animal study. In this instance, dogs may be the more appropriate species because dogs have higher exposures to KP415 than rats do (approximately 20-fold difference). In addition, if only one embryofetal development study is needed, a PK study in rabbits would be needed to determine if rats or rabbits were the most appropriate species to qualify KP415. The need for any additional nonclinical studies (for example, fertility, pre- and post-natal development, or carcinogenicity) would be dependent on the findings from the chronic toxicology and embryofetal development studies.

> ***Discussion:*** *The Sponsor stated that calculations for Vyvanse human mass balance study were based on molarity and not weight per the SBA for Vyvanse and they wanted to clarify that they would continue to base their calculations on molarity. After the meeting, we reevaluated and noted that human plasma concentrations for Vyvanse were expressed both based on molarity and weight. However, we reiterate that the need for animal studies to adequately assess KP415 for toxicity will not be based on the percentage of the levels of KP415 to the total drug-related material, as was stated in the Preliminary Comments.*

2.2 CLINICAL

Question 4: KemPharm is proposing a Phase 1 absorption, metabolism, excretion, and mass balance study with a single oral dose of radiolabeled KP415 prodrug. The protocol of this study

(Study KP415.111) is included in this briefing package. Does the Agency agree with the design of this study?

FDA Response to Question 4: *On face, the design is acceptable. However, you should consider enrolling 8 volunteers so that you can have a minimum of 6 evaluable subjects in case there are dropouts.*

Discussion: *No further discussion.*

Question 5: Assuming no safety concerns are identified, KemPharm proposes an open label safety study in subjects 6-12 years old with ADHD (Study KP415.S01). Subjects from the efficacy study (approximately 140 subjects receiving drug for 3-4 weeks) will be given the opportunity to roll over into the safety study to receive their optimized dose of open-label active drug for up to an additional 3 months. Does the Agency agree with this approach?

FDA Response to Question 5: *Allowing subjects who complete the efficacy study to enroll in the open-label safety study is acceptable. However, we recommend you complete the pharmacokinetic study in children prior to this study.*

Discussion: *No further discussion.*

Question 6: Based on the proposed clinical studies in Section 8.3 and the proposed safety database in Section 8.4, does the Agency agree that this constitutes sufficient exposure for a complete safety database?

FDA Response to Question 6: *We note that you plan to conduct the following clinical studies:*

- *Study of the effect of a high-calorie/high-fat mean on PK*
- *PK study in children (ages 6 to 12 years) and adolescent (ages 13 to 17 years)*
- *PK bridging study to Focalin XR in adults*
- *Mass balance study with radiolabeled KP415*
- *Laboratory classroom efficacy trial in children*
- *Open-label safety study in children*

You project that 451 patients will receive at least one dose of KP415, 212 patients will receive multiple doses of KP415, and 140 patients will receive at least 90 days of treatment with KP415.

Given that KP415 is an NME and that it is intended for chronic administration, you should plan to meet ICH E1 criteria for safety exposure in your development program (i.e., 300-600 patients for 6 months, 100 patients for 1 year).

Discussion: *The Sponsor stated that KP415 is inert and wanted to know if studying a population of 200 subjects for six months would be sufficient to satisfy long-term exposure requirements for this NDA. The Division responded that it will be a matter for further*

consideration after the requested non-clinical data is reviewed. The Division emphasized that our default position is to follow the guidance provided in ICH E1.

Question 7: Based on the anticipated results of the dose proportionality PK study in adults (KP415.104) and the PK study in children and adolescents (KP415.105), can efficacy and safety findings in children (6-12 years; Study KP415.E01) support efficacy and safety in all patients ≥ 6 years of age?

FDA Response to Question 7: *We are unable to respond to this question at this time. This will be a matter for review after you submit the results of these studies and provide justification why safety and efficacy can be inferred for adolescents and adults based on the available data.*

Discussion: *No further discussion.*

Question 8: Based on clinical studies summarized in Section 8.3 and completed clinical studies summarized in Section 8.2, KemPharm believes this constitutes a full clinical program sufficient for NDA filing (see Discussion in Section 8.6), assuming no safety concerns are identified. Does the Agency agree?

FDA Response to Question 8: *The adequacy of these data to support an NDA filing will be a matter for review at the time of the pre-NDA meeting and following submission of the NDA.*

Discussion: *No further discussion.*

2.3 ABUSE POTENTIAL

Question 9: Based on comments received from the End of Phase 1 Meeting (dated June 14, 2017), KemPharm proposes the in vitro tampering assessment detailed in Section 9.4. Does the Agency agree with this proposed approach?

FDA Response to Question 9: *We agree that the tampering studies are appropriate and remind you to conduct them on the to-be-marketed formulation.*

Discussion: *No further discussion.*

Question 10: Based on comments received from the End of Phase 1 Meeting (dated June 14, 2017), KemPharm intends to conduct all Human Abuse Potential (HAP) studies with only the KP415 prodrug (not formulated with d-MPH). Does the Agency agree with this approach?

FDA Response to Question 10: *We agree that the HAP studies should be conducted only on the KP415 prodrug as this is a derivative of MPH not currently scheduled in the CSA, whereas MPH is already scheduled as C-II.*

The Division of Biometrics VI is reviewing the statistical plan of the amended protocol and their recommendations will be sent to you in a separate communication.

Discussion: *No further discussion.*

Question 11: Does the Agency agree with the design, choice of positive controls, and dose selections in the proposed oral HAP study, as described in Section 9.3.2?

FDA Response to Question 11:
Qualification Phase: Please note that for qualification into the Treatment Phase, the Drug Liking VAS should be outside the placebo range and higher than 60 for Focalin treated subjects in addition to being 15 points higher for Focalin than placebo.

Justify using an IR form of Focalin for the Qualification Phase and an XR form for the Treatment Phase.

Treatment Phase: Justify the ***safety*** *of using the 120 mg and 240 mg doses of KP415 prodrug in the Treatment Phase.*

Discussion: *The Sponsor intends to use the XR formulation of Focalin for both the Treatment and Qualification Phases. The Sponsor will reconsider whether they will use 120 mg and 240 mg doses of KP415 or will provide justification for using these doses. We recommend using supratherapeutic doses for the HAP study but their safety needs to be justified.*

Question 12: Does the Agency agree with the design, choice of positive control, and dose selections in the proposed intranasal HAP study, as described in Section 9.3.3?

FDA Response to Question 12:
Qualification Phase: Please note that for qualification into the Treatment Phase, the Drug Liking VAS should be outside the placebo range and higher than 60 for MPH treated subjects in addition to being 15 points higher for MPH than placebo

Treatment Phase: Justify the ***safety*** *of using a dose of 120 mg KP415 prodrug during this phase.*

Discussion: *Please see Question 11 discussion.*

Question 13: KemPharm believes the three HAP studies outlined in Section 9.3, in addition to appropriate in vitro tampering assessments outlined in Section 9.4, constitute a full abuse potential assessment. Does the Agency agree?

FDA Response to Question 13: *A full abuse potential assessment constitutes the results of HAP studies, tampering studies, and abuse related AEs and information on drug accountability in clinical trials.*

Discussion: *No further discussion.*

Question 14: Does the Agency agree with the use of Focalin XR as an appropriate comparator in the KP415 in vitro tampering studies (Section 9.4)?

FDA Response to Question 14: *We agree that Focalin XR is an appropriate comparator for the tampering studies as it is a long acting formulation of a stimulant in the same class as KP415.*

Discussion: *No further discussion.*

2.4 CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

Drug Substance

Question 15: Does the Agency agree with the outlined development strategy for the manufacturing process for the KP415 drug substance (Section 10.1)?

FDA Response to Question 15: *Your approach appears reasonable. Please comment on the mutagenic impurity class* (b) (4) *that is found* (b) (4) *in your registration batch. The* (b) (4) *is a structural alert from our perspective.*

Discussion: *KemPharm asked whether the Agency had any specific knowledge on the mutagenic potential of the* (b) (4) *impurity. The Agency stated that they did not have any specific knowledge, but that* (b) (4) *are regarded as potential mutagens* (b) (4)*. The Agency indicated that KemPharm can provide data to demonstrate this impurity is not genotoxic. KemPharm indicated that they intended to do so.*

Question 16: Does the Agency agree with the proposed strategy for the KP415 regulatory starting materials (Section 10.1.6)?

FDA Response to Question 16: *Your proposed regulatory starting materials appear reasonable. However, please develop specifications for your starting materials that will ensure the quality of the final drug substance.*

Discussion: *No further discussion.*

Question 17: KemPharm proposes (b) (4) (b) (4) as the manufacturing process steps to be conducted under cGMP conditions (refer to Section 10.1.6). Does the Agency agree?

FDA Response to Question 17: *We do not agree. FDA considers the designation of a regulatory starting material to be the beginning of the GMP process. Therefore, all steps carried out after the designated starting material should be under GMP. Please refer to ICH Q7 for more information.*

Discussion: *KemPharm requested clarification on this point. It was agreed that the synthetic step* [redacted] (b) (4) *would be the first GMP step.*

Question 18: Does the Agency agree with the proposed control strategy for the desired stereoisomer in the KP415 structure (Section 10.1.10.3)?

FDA Response to Question 18: *Your proposed control strategy appears reasonable. We recommend developing an appropriate specification for your chiral starting materials. Please update your drug substance specification to include optical rotation if that is your intent.*

Discussion: *No further discussion.*

Question 19: Does the Agency agree with the rationale that PSD analysis of KP415 drug substance is not a critical quality attribute and thus does not need to be included in the final release specification for the KP415 drug substance (Section 10.1.10.4)?

FDA Response to Question 19: *Your rationale appears reasonable. Based on the current information, it seems more reasonable to monitor the granules.*

Discussion: *No further discussion.*

Question 20: The sponsor intends to transfer and scale-up the KP415 manufacturing process to a secondary site. Assuming no major changes will be made to the current process used for registration batches, KemPharm proposes to include 3 months of accelerated stability data for material manufactured at this site at NDA submission. Does the Agency agree that these data are sufficient to qualify this secondary site for KP415 drug substance manufacturing?

FDA Response to Question 20: *We have the following comments:*

1. *The KP-415 drug substance from a new commercial supplier should be appropriately bridged to the clinical drug substance batches. This could be accomplished by comparison of drug substance batch data (three batches from each supplier) and stability data (3 months long-term and 3 months accelerated from the new supplier).*

2. *In your NDA submission, all facilities involved in manufacturing the drug substance should be listed and must be ready for inspection at the time of NDA submission.*

3. *You should clarify the origin and the roles of your drug substance batches (toxicological, clinical, and registration batches) in your NDA submission.*

4. *As a reminder, we generally expect a minimum of 12 months long-term testing on at least three primary drug substance batches at the time of NDA submission.*

Discussion: *No further discussion.*

Drug Product

Question 21: Does the Agency agree with the proposed development strategy for the KP415 Capsules (Section 10.3)?

FDA Response to Question 21: *The proposed development strategy for the KP415 capsules appears to be reasonable, but will be a matter for review based on data provided as development proceeds. In addition, we have the following comments:*

1. *Given the proposal to sprinkle the capsule contents on food as an additional dosing route, you should perform compatibility studies across the pH range for expected dosing foods. We note that you have stated that the KP415 drug substance is not stable under basic conditions.*

2. *We recommend performing compatibility studies for the two drug substances and excipients used in the current formulations at the time of the planned NDA submission.*

3. *Photostability studies should be performed on the 30 mg strength dark blue capsules to ensure that they don't fade to the lighter blue 20 mg strength capsule color.*

4. *Note that the KP415 prodrug product's established name and dosage strength may need to be expressed in terms of the active moiety quaternary cation in accordance with Agency's salt policy guidance (Naming of Drug Products Containing Salt Drug Substances). A final decision will be made during the NDA review cycle. We recommend that a future NDA includes justification on how you express the name and strength.*

Discussion: *No further discussion.*

Question 22: Does the Agency agree with the proposed battery of tests in the proposed specification (Section 10.3.7)?

FDA Response to Question 22: *The proposed battery of tests appears to be reasonable for clinical drug product batches. At this stage of development, specified drug product acceptance limits should be provided to ensure the quality of the final drug product. Drug product impurity levels must be qualified by nonclinical toxicology studies or justification provided for proposed impurity limits. Regarding registration batches, the drug product specification HPLC identification method is not specific for the drug substance and would not be able to discriminate*

from closely related structures. Either an analytical procedure considered specific for the drug substance must be used or an orthogonal method for identification can be added to comply with ICH Q6A.

Discussion: *No further discussion.*

Question 23: Does the Agency agree with the proposed dissolution method for KP415 capsules (Section 10.3.8.2)?

FDA Response to Question 23: *We agree with the general method development approach for KP415 capsules. However, please note that we cannot fully evaluate the proposed in vitro dissolution method under an IND meeting. Therefore, we recommend that you provide the complete in vitro dissolution method development (test media, apparatus, temperature, agitation speed, etc.) and validation report under an amendment to the IND. Indicate in the cover letter that you are requesting feedback/comments on its acceptability. Alternatively, you may include the method development and validation reports in the future NDA.*

In addition, because the proposed drug product exhibits an extended-release profile, we recommend that you investigate in vitro alcohol dose dumping potential of the proposed drug product.

Please refer to the Additional Biopharmaceutics Comments for detailed recommendations on information that should be provided in the NDA regarding the development of the in vitro dissolution test and setting of the in vitro dissolution acceptance criteria for the proposed drug product.

Discussion: *KemPharm explained that the formulation is an immediate-release formulation and not an extended-release formulation. The extended-release PK profile of KP415 oral capsules is based on the intrinsic property of the prodrug molecule, and so dose dumping in the presence of alcohol is not anticipated. The FDA recommended conducting an in vitro study to confirm that the proposed extended-release KP415 capsule does not have alcohol-induced dose-dumping potential.*

Question 24: Does the Agency agree with the bracketing approach for the stability testing of the drug product registration batches due to the use of the common blend (Section 10.3.11)?

FDA Response to Question 24: *The proposed bracketing approach for the stability testing of the drug product registration batches is reasonable provided that it is carried out in accordance with ICH guideline Q1D.*

Discussion: *No further discussion.*

Question 25: Does the Agency agree with the anticipated scale-up strategy outlined in Section 10.3.4, and with corresponding stability data to be included in the NDA submission?

FDA Response to Question 25: *The drug product scale-up strategy appears reasonable. For registration batch stability, it is our expectation that the planned NDA will include at least 12 months of long-term stability data and at least 6 months of accelerated stability data at the time of submission. Although not considered a filing issue, we will evaluate the proposed expiration period based on the quantity and quality of the stability data provided in the submission. The proposed expiration period should ensure that the drug product is commercially viable. We would like to remind you that as stated in Guidance for Industry: ICH Q1E Evaluation of Stability Data, "where long-term data are not amenable to statistical analysis, the proposed shelf life can be up to one-and-a-half times as long as, but should not be more than 6 months beyond, the period covered by long-term data," if relevant supporting data are available.*

> ***Discussion:*** *KemPharm plans to have long-term stability data through 12 months on three smaller-scale registration batches of each strength. They asked whether stability data through three months on larger commercial scale (approximately 3-5 fold scale-up) would be sufficient to support batches manufactured at the commercial drug product site. The Agency indicated that this approach appears acceptable. Further, as the strengths are dose proportional, differing only in capsule fill-weight, KemPharm asked whether a bracketing approach would be acceptable – with data being provided on three batches each of the lowest and highest of the three strengths for the commercial scale drug product batches. The Agency indicated that this appeared to be an acceptable approach.*

Additional Biopharmaceutics Comments

1. ***In Vitro Dissolution Test****: Include the in vitro dissolution test method development report supporting the selection of the proposed test. This report should include the following information:*

   a. *Solubility data for the drug substance as a function of pH range and in the dissolution media.*

   b. *Because the proposed drug product is an extended-release drug product, we recommend the use of acidic and basic pH dissolution media to evaluate the extended-release in vitro dissolution profile of the proposed drug product.*

   c. *Because the proposed drug product is a capsule dosage form, we recommend that you investigate Tier I and Tier II dissolution methods with and without enzymes as noted in USP <711>.*

   d. *A detailed description of the in vitro dissolution method being proposed for the evaluation of the drug product and the developmental parameters (i.e., selection of the equipment/apparatus, ionic species and ionic strength of the dissolution media, volume of the dissolution media, filter pore size, etc.). The testing conditions used for each test*

parameter should be clearly specified. If possible, the dissolution profile should be complete and cover at least 85% of the label amount or whenever a plateau (i.e., no increase over three consecutive time-points) is reached. FDA recommends the use of at least twelve discrete dosage units per testing variable.

e. *Provide the complete dissolution profile data (individual, mean, SD, profiles) for your proposed drug product. The dissolution data should be reported as the cumulative percent (%) drug released over time.*

f. *Include the testing conducted to demonstrate the discriminating power of the selected in vitro dissolution method as well as the supportive validation data for the method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). In general, the testing conducted to demonstrate the discriminating ability of the selected in vitro dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables (e.g., drug substance particle size, solid state chemistry of the drug substance, etc.). In addition, if available, submit data showing the capability of the selected in vitro dissolution method to reject batches that are not bioequivalent.*

g. *A list of critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution profile of the proposed drug product.*

h. *Data Presentation: In the method development report, present detailed experimental data as follows:*

i. *Include individual vessel data for each drug substance as much as possible in the narrative portion of the report, particularly investigation of the selection of equipment, media, etc.*

ii. *In addition to the mean in vitro dissolution data presented in graphical and tabular formats in the development report, submit all individual vessel dissolution data for each drug substance for the clinical and registration/stability batches in ".xpt" format.*

iii. *The in vitro dissolution data for batch dissolution and stability testing for each drug substance should be presented graphically; the plot(s) of individual vessel data for the clinical and stability batches should include data at dissolution, time zero stability time point, and over the duration of stability testing under long-term storage conditions.*

2. ***In Vitro Dissolution Acceptance Criteria****: Provide the complete dissolution profile data from the clinical and stability registration batches for each drug substance supporting the selection of the in vitro dissolution acceptance criteria (i.e., specification-sampling time*

points and specification values). For the setting of the in vitro drug dissolution acceptance criteria, the following points should be considered:

a. *The in vitro dissolution specifications should encompass the timeframe over which at least 85% of the drug substance is dissolved or whenever the plateau for the drug dissolved is reached if incomplete dissolution is occurring.*

b. *The acceptance criteria ranges must be based on the overall drug dissolution data generated at these times. Because the proposed drug product exhibits an extended dissolution profile, we recommend setting the in vitro dissolution acceptance criteria at an early time-point (5-10% drug released), middle (approximately 50% drug released), and a later time-point (NLT 80% drug released) or based on the release pattern of the proposed drug product.*

c. *Data from the lots used in the clinical trials and primary stability studies must be used for setting the in vitro dissolution acceptance criteria.*

d. *In general, the selection of the in vitro dis solution acceptance criteria ranges is based on mean target value ±10% and NLT 80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.*

e. *The in vitro dissolution acceptance criteria should be set in a way to ensure consistent performance from lot-to-lot and these criteria should not allow the dissolution of any lots with dissolution profiles outside those that were tested clinically.*

Note that the final acceptability of the in vitro dissolution method is a review issue that can be determined during the IND or NDA stage. However, adequacy of the proposed in vitro dissolution acceptance criteria for your proposed drug product will be made during the NDA review process based on the totality of the provided data.

3. Alcohol-Induced Dose Dumping: *The consumption of alcoholic beverages may affect the release of a drug substance from an MR formulation. The formulation may lose its MR characteristics, leading to more rapid drug release and altered systemic exposure. This more rapid drug release may have deleterious effects on the drug's safety and/or efficacy. In vitro assessments of the drug release from the drug product using media with various alcohol concentrations should be conducted on the lowest and highest strengths of the MR drug product. The following points should be considered during the evaluation of the in vitro alcohol-induced dose dumping of MR drug products:*

a. *Dissolution testing should be conducted using the optimal apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.*

b. *The following alcohol concentrations are recommended for the in vitro dissolution studies: 0 %, 5 %, 10 %, 20 %, and 40 %.*

c. *The general considerations for the media selection are as follows:*

i. *If the optimal dissolution medium is 0.1N HCl: dissolution profiles in 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.*

ii. *If the optimal dissolution medium is NOT 0.1N HCl: dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.*

iii. *If the optimal dissolution medium has not been identified: dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (i.e., pH 1.2, 4.5, and 6.8) are recommended.*

iv. *If the dissolution of the MR product is pH-independent: dissolution data in 0.1N HCl with the above range of alcohol concentrations are sufficient.*

v. *For a delayed-release (enteric coated) product, dissolution data in 0.1N HCl with the above range of alcohol concentrations are sufficient.*

d. *The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.*

e. *The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).*

f. *The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol-induced dose dumping study should be provided to FDA for review and comment.*

Based on the results of the in vitro assessments, an in vivo BA study of the drug product when administered with alcohol may be needed.

4. ***Extended Release Claim:*** *Based on the Code of Federal Regulations, [21 CFR 320.25 (f)*], if any part of the drug product includes an extended-release (ER) component, you should provide data to support the ER claim.*

3.0 OTHER

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.

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.

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** 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.

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.

505(b)(2) REGULATORY PATHWAY

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

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

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

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

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

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

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

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

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

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

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

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

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

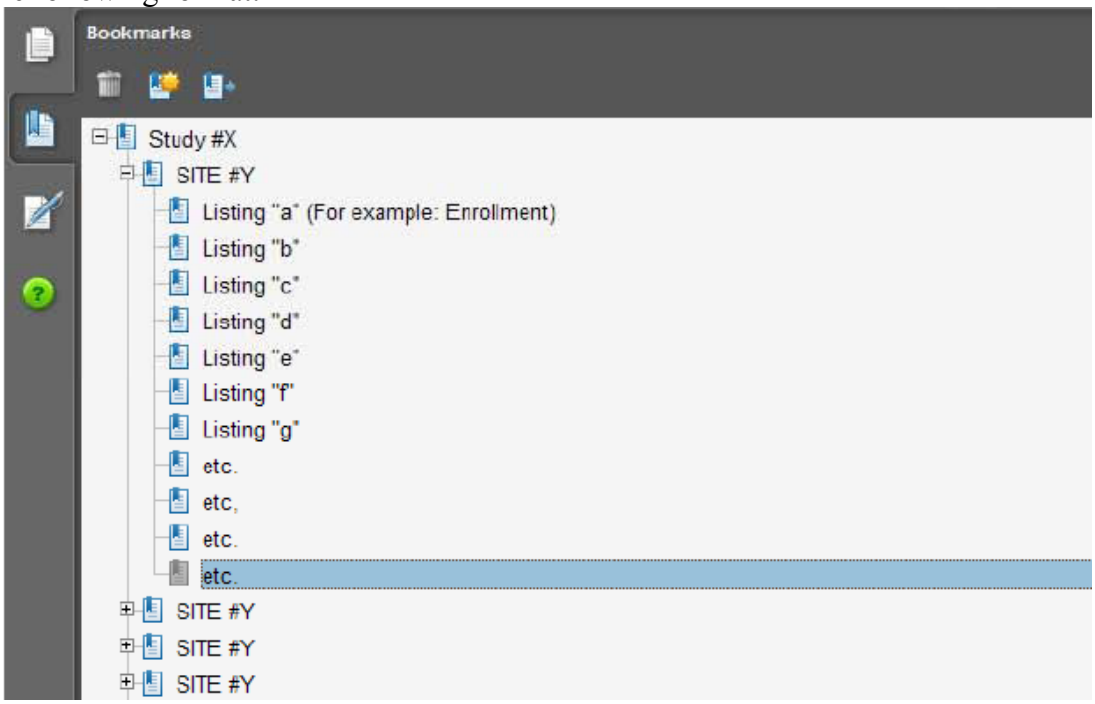
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

b. Subject listing for treatment assignment (randomization)
c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

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

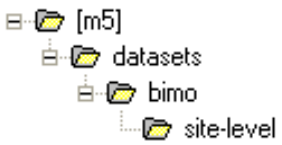
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

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

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

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

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



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

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

References:

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

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts.

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

/s/

MITCHELL V Mathis
12/14/2017