CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212038Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118297

MEETING MINUTES

Rhodes Pharmaceuticals L.P.
Attention: Todd M. Delehant, Ph.D.
Director of Regulatory Affairs
498 Washington Street
Coventry, RI 02816

Dear Dr. Delehant:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride Extended-Release Capsules.

We also refer to the meeting between representatives of your firm and the FDA on March 30, 2017. The purpose of the meeting was to gain agreement that the data intended to be included in the NDA on Chemistry, Manufacturing and Controls for PRC-063 is sufficient.

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 Teshara G. Bouie, Quality Assessment Lead (Acting), at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Wendy Wilson-Lee, Ph.D.
Branch Chief (Acting)
Branch I, Division of New Drug Products I
Office of New Drug Products
Office of Pharmaceutical Quality
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 – CMC
Meeting Date and Time:	March 30, 2017; 11:00 am -12:00 pm
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 118297
Product Name:	Methylphenidate Hydrochloride Extended-Release Capsules
Indication:	Attention-Deficit Hyperactivity Disorder (ADHD)
Sponsor/Applicant Name:	Rhodes Pharmaceuticals L.P.
Meeting Chair:	Wendy Wilson-Lee, Ph.D.
Meeting Recorder:	Teshara G. Bouie

FDA ATTENDEES
Wendy Wilson-Lee, Branch Chief (Acting)
David Claffey, CMC Lead
Rao Kambhampati, Drug Product Reviewer
Sithamalli Chandramouli, Drug Substance Reviewer
Fang Wu, Biopharmaceutics Reviewer
Kimberly Raines, Biopharmaceutics Branch Chief (Acting)
Kofi Kumi, Clinical Pharmacology Reviewer
Teshara G. Bouie, Quality Assessment Lead (Acting)

SPONSOR ATTENDEES
Rhodes Pharmaceuticals L.P.
Todd M. Delehant, Ph.D., Director of Regulatory Affairs

Purdue Pharma Canada
Sailaja Bhaskar, PhD, Sr. Director, R&D Projects and Clinical Research
Lance Payne, PharmD, Vice President, Regulatory Affairs
Maria Boulanger, BSc., Manager, Regulatory Affairs
Tushar Dave, M.S., Formulation Scientist, Pharmaceutics and Analytics

(b) (4)

(b) (4)

1.0 BACKGROUND

IND 118297 is being developed for the once daily treatment of attention-deficit hyperactivity disorder (ADHD). On January 30, 2017, the Sponsor submitted a Type B End-of-Phase 2 CMC meeting to obtain agreement that the data intended to be included in the NDA on Chemistry, Manufacturing and Controls for PRC-063 is sufficient. The sponsor is also seeking to obtain FDA's feedback on the bridging strategy and the proposed content and format of the PRC-063 NDA. Background packages were received on February 28, 2017. FDA sent Preliminary Comments to the sponsor on March 28, 2017.

2. DISCUSSION

Question 1: Does the Agency agree that comparative dissolution profile data, comparative long-term and accelerated stability data, and a bridging bioequivalence study on one batch of bulk beads are sufficient to qualify Site 2 for the manufacture of PRC-063 capsules?

FDA Response:
Refer to response to Question 1b.

Meeting Discussion: No further discussion at the meeting.

Question 1a: Does the Agency agree that inclusion of both drug substance manufacturers ((b) (4) ***) in the NDA is acceptable?***

FDA Response:
In the NDA, provide batch analysis data for batches of the drug substance from each drug substance supplier that show equivalency of chemical and physical properties of drug substance lots from both suppliers. In addition, submit stability data sufficient to justify the proposed retest period in the NDA or reference this data in any supporting DMFs.

Review of DMF # (b) (4), and other DMFs referenced therein to support the NDA, will be done as part of the NDA review.

Meeting Discussion: No further discussion at the meeting.

Question 1b: Does the Agency agree that the data as described above is sufficient to support the change of capsule composition from (b) (4) ***to*** (b) (4) ***?***

FDA Response:
No, we do not agree that the data described is sufficient to qualify Site 2 (US), including the change of composition from (b) (4) to (b) (4), for the manufacture of the PRC-063 Methylphenidate HCl ER Capsules.

The following data is recommended to be submitted during the NDA stage to support the proposed changes.

A bridging in vivo bioequivalence study for the highest strength ((b) (4) mg) of the drug product (comparing your intended commercial drug product manufactured at the US site ((b) (4) capsules) to that manufactured at the Canadian site ((b) (4) capsules)), and a request for waiver of in vivo bioequivalence bridging studies for all lower strengths with the submission of following data: (1) data showing all strengths are compositionally proportional, (2) data showing in vitro dissolution profiles of all strengths are similar, (3) data demonstrating bioequivalence on the highest strength, (b) (4) mg Methylphenidate Hydrochloride Extended-Release Capsules (comparing your intended commercial drug product manufactured at the US site and that manufactured at the Canadian site used in the pivotal clinical trials), and (4) data demonstrating dose proportionality for this ER drug product. In the last circumstance (4), documentation of dose proportionality may not be necessary if bioequivalence has been demonstrated on the highest ((b) (4) mg) and lowest strength (25 mg) of the drug product.

In the bioequivalence study, you should compute the following partial AUCs in addition to Cmax and AUC(0-inf): AUC(0-3hrs), AUC(3-7 hrs) and AUC(7 – t hrs). The 90% confidence intervals (CI) of the geometric mean test/reference (T/R) ratios for the above PK metrics should fall within the limits of 80 – 125%.
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320005.pdf

In addition, in support of your site change, in vitro dissolution profiles similarity testing should be documented for all strengths. We recommend including the following data in your NDA submission:

In addition to the application release requirements, submit data of multipoint dissolution profiles obtained using application test conditions for the changed drug products (intended commercial drug product manufactured at the US site) and unchanged drug product (drug product manufactured at the Canadian site used in the pivotal clinical trials) for all the strengths. Multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the unchanged drug product. Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or a plateau is reached.

In addition to the dissolution information, we recommend including comparative batch analysis and stability data for three batches of the (b) (4)-based drug product at each of the proposed commercial drug product manufacturing site(s) given the limited amount of commercial

manufacturing experience and higher product quality risk associated with the modified release dosage form. To the extent possible, include drug substance sourced from both proposed commercial drug substance suppliers in the registration drug product stability batches. Please list all facilities in the submission.

Meeting Discussion: The sponsor will conduct a BE study on the (b) (4) mg capsules with product from the US site ((b) (4) capsules) and the Canadian site ((b) (4) capsules instead of (b) (4) capsules) as (b) (4) capsules manufactured at Canadian site have been used in pivotal clinical trials. The Agency accepted the proposed plan. The sponsor stated that the (b) (4) capsule drug product is stable for 36 months.

Question 1c: Does the Agency agree that the difference in the quantity of the excipient silicon dioxide ((b) (4)) in these two batches of PRC-063 (b) (4) capsules compared to the intended commercial batches represent a Level 1 change under the SUPAC Guidance for Modified Release Solid Oral Dosage Forms and that the proposed stability data will support the change to (b) (4) capsules?

FDA Response:
Provide a table showing a comparison of the components and composition of the two batches of PR063 (b) (4) capsules with the intended commercial batches. The stability data generated on the current two batches of PRC-063 (b) (4) capsules may be submitted as supportive data, however, for the NDA registration, we recommend including stability data on those batches that are representative of the proposed commercial product.

Meeting Discussion: The change in (b) (4) is considered a Level 1change, however the site transfer is a Level 3 change and all submitted information should support a Level 3 change.

Question 2: Does the Agency agree with this stability plan?

FDA Response:
See responses to questions 1b and 1c. Include in the submission sufficient stability data on the (b) (4) to support any proposed (b) (4) beyond what is acceptable under current Good Manufacturing Practices.

Meeting Discussion: No further discussion at the meeting.

Question 3: Does the Agency agree that this is sufficient testing to cover testing (b) (4)

FDA Response:
No, we do not agree. (b) (4) you should still demonstrate that Class 1 and Class 2 heavy metal impurities are controlled within

ICH Q3D limits (b) (4)
Refer to the response to Question 1a regarding establishing equivalence of the drug substance lots from the two sources.

Meeting Discussion: No further discussion at the meeting.

Question 4: Does the FDA agree that the observed levels of total residual monomers and the specification of NMT (b) (4) ***ppm are acceptable?***

FDA Response:
We recommend reporting the contents of individual monomers and total monomers. The total monomers content should be tightened on the basis of the total individual monomers content. Final determination of the limit will be a review issue.

Meeting Discussion: No further discussion at the meeting.

Question 5: Although the final decision will be a review issue, does FDA agree, in principle, that the body of stability data intended to be submitted in the NDA and supplemented shortly afterward would be sufficient to support a proposed 24-month shelf-life for the drug product from both the Canadian (Site 1) and the US (Site 2) Supply Chains?

FDA Response:
Expiration dating period will be determined after a complete review of the stability data and statistical analysis of the real time data. On the basis of 12 months long term and 6 months accelerated real time stability data and statistical analysis of the data, 18 to 24 months of expiration dating period could be granted provided the number of batches and bracketing and matrixing approach are acceptable.

Meeting Discussion: At the time of submission, the sponsor will submit 2 batches from the Canadian site with 9 months stability data updated to 12 months after filing. Additionally, the submission will include 3 batches from the US site with 3 months of stability data updated with 6 months stability data after filing.

The sponsor was advised to submit a bracketing/matrix plan to the IND for the Agency's review prior to initiating the registration stability program.

Question 6: Does the FDA agree with this approach and agree that this calculation methodology does not require new validation of the dissolution analytical methodology used during the determination of the amount of methylphenidate HCl?

FDA Response:
We recommend continued use of the peak area of methylphenidate HCl only to calculate the *in vitro* dissolution results. We do not recommend the inclusion of (b) (4)

[redacted] (b) (4) , we recommend exploration of a different medium that is suitable for the proposed drug product.

[redacted] (b) (4) using the generally accepted two stage dissolution media (first acidic then basic buffer medium with pH<7.4) for ER product could help mimic the GI tract conditions and develop a bio-predictive dissolution method.

Meeting Discussion: The sponsor was advised to submit a full dissolution validation report to the IND prior to the NDA submission. Once received, the Agency will provide a timeline for review. The Agency reiterated that including [redacted] (b) (4) in the assay calculation for the dissolution method is not recommended.

ADDITIONAL COMMENTS

We have the following additional comments with regard to the drug product specifications:

1. Presently you report separate tables for finished product release and stability specifications. We recommend reconciling these two, separate tablets into one table with one set of acceptance criteria for both release and stability and clear identification of tests conducted at release only and tests considered stability-indicating.

2. Per ICH Guideline, the current identification test method is not specific for methylphenidate hydrochloride, therefore, please include an additional identification method or add photodiode array detection in the current HPLC method.

3. Include a test(s), with appropriate acceptance criteria, for microbiological quality control.

4. Include a test, with appropriate acceptance criterion, for any residual solvents, if applicable.

We have the following additional comments from biopharmaceutics perspective:

- **General Comments For Dissolution Method Development:**

The general recommendations from the Agency for the development of dissolution method are: when you develop your dissolution method, provide the following dissolution information/data in your NDA submission.

a. Provide solubility versus pH plot and data for the drug substance covering the pH range (i.e. from 1.0 to 8.0);
b. Detailed description of the developmental parameters used to select the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink

conditions, etc.). Please notice that the dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;

c. Provide the complete dissolution profile data (individual, mean, standard deviation or CV% and profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and f_2 values should be provided for the dissolution profile similarity comparison whenever needed;
d. The supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.) should be provided in Session 3.2.P.5.3 Validation of Analytical Procedures;
e. Submit data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing or material variables (i.e. ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

- **General Comments for Setting Dissolution Acceptance Criteria:**

For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

a. The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).
b. Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).
c. A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least 80% of drug has release. If the maximum amount release is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.

- **General Comments for Alcohol-Induced Dose Dumping Studies for Your Final ER Drug Product:**

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:

   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.

   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.

   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.

   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.

   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.

- **General Comments for Extended Release Claim for Your Final ER Drug Product:**

Per the Code of Federal Regulations [21 CFR 320.25 (f)], provide data to support the extended-release claim for the proposed drug product.

Meeting Discussion: No further discussion at the meeting.

From page 36 of the Meeting Package:
Does the FDA agree to the proposed approach for packaging of the registration stability batches?

Meeting Discussion: The proposed packaging plan described for the NDA registration batches is acceptable; however, since those batches are not packaged using the intended commercial process, include a commitment to place the first three commercial batches on long-term and accelerated stability as part of the post-approval stability commitment. We remind you that the planned switch from (b) (4) to (b) (4) packaging post-approval will represent a change in manufacturing process that should be reported to Agency in accordance with 21 CFR 314.70.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

Action Item/Description	Owner
Submit a bracketing/matrix plan to the IND for the Agency's review prior to submission of the NDA.	Sponsor
Submit a full dissolution validation report to the IND prior to the NDA submission.	Sponsor

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

TESHARA G BOUIE
04/12/2017

WENDY I WILSON-LEE
04/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118297

MEETING MINUTES

Rhodes Pharmaceuticals L.P.
Attention: Todd M. Delehant, PhD
Director of Regulatory Affairs
498 Washington Street
Coventry, RI 02816

Dear Dr. Delehant:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PRC-063.

We also refer to the meeting between representatives of your firm and the FDA on December 1, 2016. The purpose of the meeting was to discuss the development plan for PRC-063 for the treatment of attention deficit hyperactivity disorder (ADHD).

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, contact Dr. Brendan Muoio, Sr. Regulatory Project Manager at (240) 402-4518 or brendan.muoio@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:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	December 1, 2016, from 9 a.m. to 10 a.m. EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 118297
Product Name:	PRC-063
Indication:	Treatment of ADHD
Sponsor Name:	Rhodes Pharmaceuticals L.P.
Meeting Chair:	Mitchell V. Mathis, MD Director, Division of Psychiatry Products (DPP)
Meeting Recorder:	Brendan Muoio, PharmD, RAC Sr. Regulatory Project Manager, DPP

FDA ATTENDEES

Mitch Mathis, MD	Director, DPP
Jasmine Gatti, MD	Clinical Team Leader, DPP
Graciela Gonzalez, MD	Clinical Reviewer, DPP
Ikram Elayan, PhD	Pharmacology/Toxicology Supervisor, DPP
Deepa Rao, PhD	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biometrics (OB)
Yang Wang, PhD	Biometrics Reviewer, OB
Shalini Bansil, MD	Reviewer, Controlled Substance Staff (CSS)
Brendan Muoio, PharmD, RAC	Sr. Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Akwete Adjei, PhD	Executive Director, R&D, Rhodes Pharmaceuticals, L.P.
Richard Fanelli, PhD	Head of Regulatory Affairs, US Regulatory Affairs, Purdue Pharma L.P.
Sailaja Bhaskar, PhD	Sr. Director, R&D Projects and Clinical Research, Purdue Pharma Canada

Mossa Christine — Director, Regulatory Affairs, Purdue Pharma Canada
Lance Payne, PharmD — VP, Regulatory Affairs, Purdue Pharma Canada
(b) (4)
(b) (4)

1.0 BACKGROUND

Rhodes Pharmaceuticals L.P. (Rhodes), in collaboration with their partner, Purdue Pharma Canada, is developing an extended-release methylphenidate product (PRC-063) (b) (4) for the treatment of ADHD. (b) (4) Methylphenidate (MPH) is a central nervous system (CNS) stimulant. The mode of therapeutic action in ADHD is not known. MPH is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

PRC-063 capsules contain multi-layer beads designed with immediate- and controlled-release components. According to the Sponsor, the immediate-release (IR) layer contains 20% of the total MPH dose, with 80% of the MPH dose in the controlled-release (CR) layer. The CR component has a (b) (4) Based on pharmacokinetic (PK) studies to date, the Sponsor states that plasma MPH concentration reaches an initial maximum approximately 1.6 hours after PRC-063 administration, followed by a moderate decline in MPH concentration, then a gradual increase in MPH concentration after 4 to 6 hours, resulting in a second peak approximately 12.5 hours after dosing.

The Division provided early feedback on this development program via written responses to a pre-IND meeting request (June 14, 2013), as well as clinical comments included in the May Proceed letter (February 26, 2014) after the IND was submitted. In those communications, the Division emphasized that at least one efficacy and safety study in children ages 6 to 11 years would be required, and that such a study would need to be preceded by a PK study to inform dosing. The Division also noted that we do not consider the (b) (4) score to be acceptable as the primary efficacy measure (b) (4); the Division recommended the Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP) instead.

The PRC-063 development program to date consists of the following studies (all conclusions are as reported by the Sponsor):

- Pilot PK studies: 063-001 (n=12), 063-002 (n=12), 063-003 (n=15), and (b) (4). The time-course of d-MPH absorption from 063-003 Test 1 formulation was determined to be optimal, and this formulation was further developed.

- 063-004: Single-dose PK and food effect study in healthy adults (n=30) to characterize the PK profile of PRC-063 (100 mg) versus 60 mg immediate release (IR) MPH (20 mg three times daily). No food effect was observed.
- 063-005: Single-dose PK study in healthy adults (n=30) comparing PRC-063 administered intact or sprinkled over food. Bioequivalence was demonstrated between the intact capsule and the sprinkled contents on applesauce, yogurt, or ice cream.
- 063-006: Single-dose PK study in adolescents with ADHD (n=17, ages 12 to 17) to characterize the PK profile of PRC-063 versus IR MPH administered three times daily. The study demonstrated that the extent of absorption of PRC-063 was comparable to IR MPH administered three times daily, but the rate of absorption was lower.
- 063-007: Multiple-dose PK study in healthy adults (n = 21) to characterize the PK profile of PRC-063 100 mg administered once daily versus IR MPH 20 mg three times daily. The rate and extent of absorption of MPH from once daily PRC-063 100 mg was lower than from IR MPH 20 mg three times daily when administered for five consecutive days.
- 063-008: Randomized, double-blind, placebo-controlled, cross-over study in adults with ADHD (n=59) to characterize efficacy at a number of time points throughout a single testing day (16-hour period). Subjects treated with PRC-063 70-100 mg/day had significantly improved attention compared to placebo as measured by the PERMP in a simulated adult workplace environment. Onset of action was within one hour of receiving PRC-063, with the duration of effect continuing for up to and including 11 hours post-dose.
- 063-009: Multiple dose, randomized, double-blind, forced-dose titration, placebo-controlled, parallel-group study in adolescents with ADHD (n=367, ages 12 to 17) to evaluate efficacy and safety. Subjects were randomized 1:1:1:1:1 to one of five treatment groups (25, 45, 70, 85 mg or placebo) and received PRC-063 or placebo for 20 to 40 days. Subjects in the PRC-063 treatment arms showed greater improvement in hyperactivity, impulsivity, and inattention. Adverse events (AEs) were similar to those described in approved MPH labeling. The most common AEs in PRC-063 subjects were decreased appetite (20.1%), headache (15.0%), irritability (8.2%), decreased weight (7.5%), and insomnia (6.5%).
- 063-010: Multiple-dose, randomized, double-blind, forced-dose titration, placebo-controlled, parallel-group study in adults with ADHD (n=375, ages 18 to 72) to evaluate efficacy and safety. Subjects were randomized 1:1:1:1:1 to one of five treatment groups (25, 45, 70, 85 mg or placebo) and received PRC-063 or placebo for 20 to 40 days. Subjects in the PRC-063 treatment arms showed greater improvement in hyperactivity, impulsivity, and inattention. Adverse events were similar to those described in approved MPH labeling. The most common AEs in PRC-063 subjects were headache (17.5%), insomnia (15.8%) and decreased appetite (11.1%).
- 063-012: An open label, multi-center, six-month study to evaluate the long-term safety and efficacy of PRC-063 in adolescent (n=176, ages 12 to 17) and adult subjects (n=184, age ≥ 18) with ADHD who completed either 063-009 or 063-010. PRC-063 25, 35, 45, 55, 70, 85 or 100 mg oral capsules were administered once-daily in the morning. The maximum dose was 85 mg/day for adolescents and 100 mg/day for adults. The most common AEs were headache (12.9%), insomnia (12.9%) and decreased appetite (11.3%).
- 063-013: A randomized, double-blind, crossover study comparing two long-acting stimulant formulations, once-daily PRC-063 and once-daily lisdexamfetamine (LDX),

through a 15-hour period on driving performance, as measured with a driving simulator, in adult patients with ADHD (n = 45). This study is ongoing.

Planned Phase 3 Study:

063-015: A randomized, double-blind, placebo-controlled, [redacted] laboratory classroom study to evaluate the safety and efficacy of PRC-063 in children (ages 6 to 12) with ADHD.

The study will have [redacted] phases:

1. [redacted] week screening and subsequent washout, if needed;
2. an [redacted] week, open-label dose-optimization phase during which subjects will be titrated from a starting dose of 25 mg up to his/her optimal dose (25, 35, 45, 55, 70 and 85 mg/day);
3. [redacted] week double-blind [redacted] phase which will include [redacted] in an analog classroom.
4. [redacted]-day safety follow-up. [redacted]

The planned primary efficacy endpoint is the SKAMP. Secondary endpoints include [redacted]

The Sponsor intends to request a waiver for pediatric studies in patients ages [redacted] years and younger, [redacted].

The Sponsor requested this End-of-Phase 2 meeting to discuss the development plan for PRC-063 for the treatment of ADHD. Their stated objectives for this meeting are to gain agreement on the following:

- The overall clinical, clinical pharmacology and non-clinical development plan to support the filing and approval of PRC-063 for the indication of "treatment of ADHD in [redacted] years and older" and the use of Concerta® and Ritalin® IR as Reference Listed Drugs (RLDs) to support a New Drug Application (NDA) filing via the 505(b)(2) regulatory pathway.
- Adequacy of the safety database.
- Acceptance of the [redacted] described in the Draft Guidance "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products" (FDA 2014).
- [redacted]

FDA sent Preliminary Comments to Rhodes on November 29, 2016.

2.0 DISCUSSION

2.1. Nonclinical

Question 1: Does the Agency agree that nonclinical data available on [redacted] provide sufficient exposure to cover a clinical dose above [redacted] mg per day?

FDA Response to Question 1: The Summary of Safety Data for [redacted] includes brief summary statements from multiple nonclinical toxicology studies conducted with [redacted] by the supplier. The data from these nonclinical toxicology studies will need to be reviewed for safety prior to Phase 3 clinical studies to determine whether the use of [redacted] at the proposed clinical dose levels of up to [redacted] mg per capsule is acceptable.

The complete toxicology studies may be submitted to the Drug Master File (DMF) along with a Letter of Authorization from the supplier to access these studies. In addition, if any published studies are publically available, citations and references can also be submitted. The NDA 505(b)(2) application can rely on the Right of Reference to the DMF and/or published literature.

Discussion: *There was no further discussion.*

Question 2: Does the Agency agree that the overall nonclinical program described below is sufficient to support filing and approval of PRC-063 for the proposed indication?

FDA Response to Question 2: Based on the long history of use of MPH, and on the proposed 505(b)(2) pathway referencing Concerta® and Ritalin®, we do not anticipate a need for additional nonclinical studies.

However, the determination of safety for [redacted] is contingent upon review of the nonclinical toxicology studies as stated above (see response to Question 1).

In addition to MPH, a complete literature search will need to be completed on all synonyms for [redacted] such as [redacted].

Any other unanticipated events such as changes in formulation, issues with excipients, impurities and/or degradants that exceed ICH thresholds may need to be reduced or qualified in appropriate non-clinical studies. We refer you to the ICH Guidelines Q3A(R2) and Q3B(R2) for additional information on impurity qualification.

Discussion: *There was no further discussion.*

Question 3: Does the Agency agree in principle that Section 8 (8.1 and 8.4) and Section 13 of the PRC-063 label will present language adopted from RLD labels (Concerta® and Ritalin®)?

FDA Response to Question 3: In principle, we agree. However, all NDAs submitted on or after June 30, 2015, including 505(b)(2) applications, are required to be in Pregnancy and Lactation Labeling Rule (PLLR) format at the time of submission. Please refer to the GENERAL GUIDANCE section of this letter for additional information on PLLR format.

Discussion: *There was no further discussion.*

2.2. Clinical Pharmacology

Question 4: Does the Agency agree that data generated from the in vitro alcohol study RD-R-MPX-15-01 is sufficient to support filing and approval of PRC-063?

FDA Response to Question 4: We agree that the provided results from the PRC-063 in vitro ethanol study showing that 61% of drug is released at 2 hours with 40% ethanol and your justification with precedence of other approved extended-release MPH products would support the filing of your proposed PRC-063 product without an additional study in humans. However, be aware that the final acceptance of the results from the in vitro alcohol study RD-R-MPX-15-01 and the regulatory decision will be determined at the NDA stage. Given that alcohol may exacerbate the adverse CNS effects of stimulant drug products including MPH, you should propose appropriate labeling language with your NDA submission to address the concern of concomitant alcohol consumption.

Discussion: *There was no further discussion.*

Question 5: Does the Agency agree that the clinical pharmacology program described in the briefing document is adequate and no further clinical pharmacology studies are required for filing and approval of PRC-063?

FDA Response to Question 5: On face, the clinical pharmacology studies conducted are acceptable. However, the acceptability of the findings is a review issue. In addition to the conducted clinical pharmacology studies, we recommend that you assess the effect of changes in gastric pH on drug release (b) (4). A typical way to assess this effect is to conduct an in vivo drug interaction study with a gastric pH modulator (e.g., a proton pump inhibitor with no expected interaction with MPH metabolism). Because of the significant delay of drug release from the modified-release layer, we recommend that you also address how changes in gastrointestinal mobility (e.g., bowl movement) may affect the PK profile.

The degree of contribution to the safety and efficacy of MPH by the l-isomer is unclear. You should include the exposure levels of the l-isomer of MPH after administration of your product compared to the reference drug in your final study reports submitted in the NDA. You may also rely on available clinical pharmacology data from the reference listed drugs to support your application.

Discussion: *The Sponsor stated that* (b) (4) *. In addition, the Sponsor agreed* (b) (4)

Question 6: Does the Agency agree in principle that the proposed label will present PRC-063 clinical pharmacology data in Sections 2, 7, 8 and 12 along with additional language adopted from the labels of the RLD (Ritalin® IR and Concerta®)?

FDA Response to Question 6: Generally, yes we agree. However, whether Clinical Pharmacology information should be included in other sections (e.g., Warnings and Precautions), is a review issue. In addition, Clinical Pharmacology information is included in the Highlights of the label.

Discussion: *There was no further discussion.*

Question 7: (b) (4) , does the Agency agree that (b) (4) is appropriate for filing and approval of PRC-063?

FDA Response to Question 7: No, we do not agree. (b) (4) a PK study in children 6 to 11 years-old is needed to confirm that exposure levels are equivalent and consistent with the simulation results.

Discussion: *The Division clarified that a PK study would be used to ensure a similar PK profile between children and adolescents as well as to inform dosing considerations for study 063-015.* (b) (4) .

The Division strongly recommended that the PK information be collected prior to the initiation of the efficacy and safety study. Specifically, the Sponsor should assess whether the T_{max} for the second peak MPH concentration will be different in patients 6 to 11 years compared to adolescents or adults, or whether a sufficiently high concentration will be presented between 12 and 24 hours post dose.

If the topline PK information can be obtained within a sufficiently short time, the Sponsor may include the PK evaluation as a PK lead-in phase in the pediatric efficacy and safety trial.

Post-meeting comments: *The Sponsor should define clear criteria to inform potential dosing changes or stopping criteria for the efficacy and safety phase of the trial when different PK results are seen. If these criteria are agreed to by the Division, the Sponsor may proceed to the efficacy and safety phase without further interaction with the agency.*

2.3. Clinical

Question 8: Does FDA agree that the safety database at filing will be adequate to support filing and approval of PRC-063 for the proposed indication based on the completed clinical pharmacology studies, and the completed Phase 3 program along with known experience from previously approved methylphenidate products?

FDA Response to Question 8: On face, it appears that the safety database will be adequate for adolescents and adults. Safety data for patients younger than 12 years-old will still be required (see Question 11).

Discussion: *There was no further discussion.*

Question 9: Does FDA agree that the proposed label will present the safety data from the PRC-063 development program in Sections 4, 5 and 6 along with additional language adopted from the RLD (Ritalin® and Concerta®) labeling as outlined in Appendix 1 of the briefing document?

FDA Response to Question 9: Your overall plan for labeling appears reasonable; the acceptability of specific labeling language will be a matter of review when the NDA is submitted.

Discussion: *There was no further discussion.*

Question 10: Does FDA agree that the overall clinical program represents an adequate safety and efficacy package to support filing and approval of PRC-063 for the proposed indication?

FDA Response to Question 10: Please see our comments below regarding studies in children ages 6 to 11 years.

Discussion: *See discussion for Question 11.*

Question 11: If the Agency does not accept (b) (4), does the Agency agree with the following design elements of the proposed analog classroom

study (Study 063-015)? Will conducting this study enable Rhodes to get the indication in children 6-11 years of age?

FDA Response to Question 11: (b) (4) *. We suggest you continue with your Phase 3 study in this population (6-11 years of age) with multiple fixed doses. We do not agree with the overall design of your study in children 6 to 11 years of age and we will need more specific details on your design. We suggest that you include subjects from this age range in a six-month, long-term, fixed-dose study to evaluate safety.*

Additionally, the analog classroom study protocol (063-015) needs to specify exactly what the primary and secondary endpoints will be. Also you need to describe how you intend to calculate them (e.g., measuring at onset and offset on the medication, measuring the overall effect throughout the day, etc.).

(b) (4)

We will provide additional comments after review of the full study protocol.

Discussion: *The Sponsor explained that they do not believe that a fixed-dose study would be appropriate based on current ADHD guidelines and clinical practice and, instead, proposed a dose-optimized study, stating that this design would be more in line with real life use. The Division agreed that the proposed study design would reflect a more real life setting, but that the use of fixed doses would allow for adequate safety data to inform product labeling. The Division noted that the difference in formulation compared to other MPH products warrants the need for additional safety information, and that the requested six-month, fixed-dose study would be more appropriate to accomplish this. The Sponsor proposed to* (b) (4) *in lieu of conducting the fixed-dose study. The amended protocol and statistical analysis plan will be submitted for review.*

The Sponsor also enquired about the possibility of obtaining an efficacy claim for children ages 6 to 11 years of age if study 063-015 was positive. The Division indicated that it would be open to this possibility, but that it would be a matter of review.

2.4. Abuse Liability Potential

Question 12: Rhodes plans to rely on the extensive published literature and experience in the abuse potential of methylphenidate for a future NDA filing. Does the Agency agree that this will enable an assessment of abuse potential as described in the January 2010 FDA Draft Guidance for Industry, "Assessment of Abuse Potential of Drugs"?

FDA Response to Question 12: Your proposal is currently under review with CSS. Comment will be provided during the scheduled End of Phase 2 meeting.

Discussion: *CSS agreed with the Sponsor's proposal and stated that it should allow for a meaningful review at the time of the NDA filing. They recommended that the Sponsor make sure that all study reports, and links to those reports, are included in the NDA submission. The incidence of abuse-related AEs in comparison to placebo in trials already conducted should be reported by study, population, and dose, and displayed in tabular format. Tables should be created for abuse-related, higher-level terms even if there were few patients or subjects who experienced a particular AE.*

Question 13: Does FDA agree in principle that Section 10 of the proposed label for PRC-063 will adopt language from the RLD labeling as outlined in Appendix 1 of the briefing document?

FDA Response to Question 13: Your proposal is currently under review with CSS. Comment will be provided during the scheduled End of Phase 2 meeting.

Discussion: *CSS deferred labeling preference for Section 10 to the Division. The Division indicated that the Sponsor's proposal was acceptable on face, but that it will be a matter of review.*

2.5. Pediatric Development Plan

Question 14: Provided in Appendix 3 is the draft initial Pediatric Study Plan (iPSP) as required under PREA Requirements. Rhodes is requesting a partial waiver of pediatric assessments for ages 0-(b) (4) years (b) (4) . The final PSP will be filed to the IND within 60 days of this meeting. Does FDA agree with Rhodes Pharma's approach to fulfill PREA requirements?

FDA Response to Question 14: No, (b) (4) . A partial waiver for children under 4 years of age is reasonable. We will provide further comment after the iPSP is submitted.

Discussion: *The Sponsor expressed concern that a safety and efficacy study would not be appropriate in (b) (4) year olds. The Division agreed that no PK study will be needed in pediatric patients (b) (4) years of age if the Sponsor's request for a waiver is granted. The*

Sponsor plans to include a waiver request for children, ages 0 to (b) (4) *years of age in their iPSP submission. Whether such a waiver is granted will be a matter of review.*

2.6. Additional Questions

Question 15: Based on the data presented and the FDA's experience with approved methylphenidate and amphetamine and non-stimulant compounds for the proposed indication, does the Agency have any additional feedback on the proposed development program?

FDA Response to Question 15: We do not have additional feedback to provide at this time.

Discussion: *There was no further discussion.*

3.0 GENERAL GUIDANCE

PREA REQUIREMENTS

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

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

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

PREGNANCY AND LACTATION LABELING RULE

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

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

DATA STANDARDS FOR STUDIES

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

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

implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft

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

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

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

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

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

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

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

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

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

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

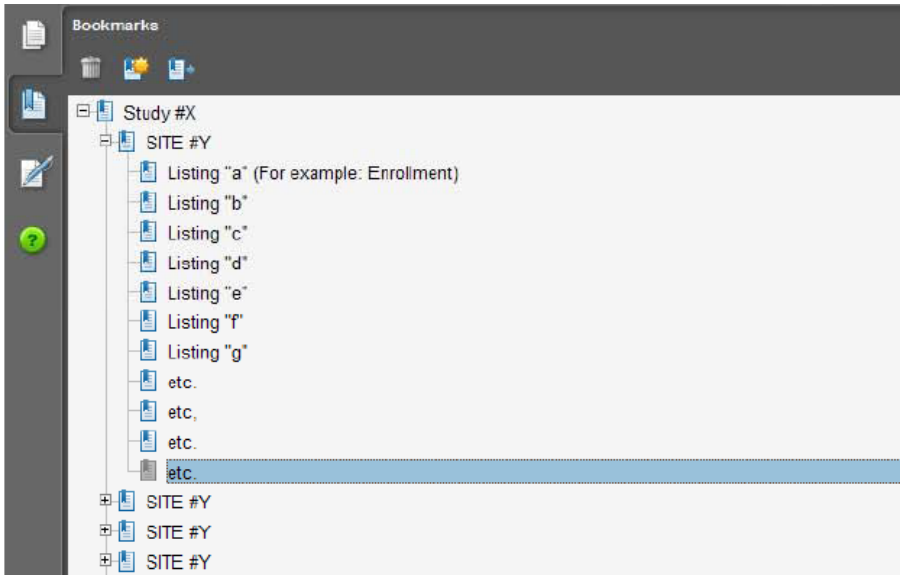
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

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

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.

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.

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
12/30/2016