

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209311Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



NDA 209311

**APPEAL GRANTED**

Ironshore Pharmaceuticals & Development, Inc.  
c/o Baker Botts L.L.P.  
Attention: Margaret Sampson  
US Agent  
98 San Jancinto Boulevard, Suite 1500  
Austin, TX 78701

Dear Ms. Sampson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for methylphenidate hydrochloride modified release (HLD200), 20, 40, 60, 80, and 100 mg. capsules.

I also refer to your request for formal dispute resolution (FDRR) submitted and received on March 27, 2018. The appeal concerned the complete response (CR) action taken on this NDA by the Division of Psychiatry Products (DPP) on July 28, 2017.

I also refer to the post-action meeting held between FDA and Ironshore Pharmaceuticals and Development, Inc. on April 25, 2018, where the safety concerns that formed the basis for the CR action were further discussed, along with additional issues you raised that were not a basis for the CR action.

Ellis Unger, M.D., has delegated your Office of Drug Evaluation I level appeal to me, the Deputy Director of the Office of Drug Evaluation I.

I have carefully reviewed the materials you submitted in support of your appeal, as well as reviews, meeting minutes, and decision memoranda prepared by FDA staff along with the complete response letter. I have also consulted with Staff in the Division of Psychiatry Products, and Division of Epidemiology I.

I have completed my review of your FDRR and grant your appeal that the studies you submitted would support approval of HLD200 for the treatment of ADHD. I note, however, that your request to describe (b) (4) in labeling is outside the scope of FDR, as a final decision on that matter was not made. Because DPP's safety concerns

led to a CR action, labeling claims were not decided upon or included in the action. I further describe below the basis for my decision.

The CR letter for HLD200 sent to you on July 28, 2017, by DPP was based on what appeared to be an unusually high rate of insomnia (almost 36%) in the drug-treated group compared to 13.8% in the placebo-treated group in Study 108. No similar excess was present in Study 107. The increased insomnia represented a potential problem for the delayed-release product, which is taken in the evening before sleep. If some of the drug were to be released early, insomnia would be an anticipated result.

In your FDRR, you argued that the high insomnia rate in Study 108 was the result of the study design, which did not include the usual open-label dose-optimization run-in period, with randomization of only patients who tolerated the drug, but instead used a forced-titration design, which would capture all insomnia events (even early ones that did not persist). This contrasted with the traditional design, where events leading to discontinuation prior to randomization would not be counted.

The data from both trials in this program are presented below. I note that Study 107, which used the more traditional design with open label titration prior to randomization, showed a total insomnia adverse event rate of 34.2%, which is similar to the rate in Study 108 (35.85%) when the open label period is included. There were, however, much lower rates in the double-blind period and no drug-placebo difference. Perhaps more important, results of several pharmacokinetic studies (in adults with the to-be-marketed formulation and in children using an earlier formulation) demonstrated no appreciable drug release during the overnight period.

#### Number (Percent) of Patients Reporting Insomnia

| Study 107         |                     |         |               | Study 108           |          |               |
|-------------------|---------------------|---------|---------------|---------------------|----------|---------------|
| Open-label Period | Double-blind Period |         |               | Double-blind period |          |               |
| HLD200            | HLD200              | Placebo | Relative Risk | HLD200              | Placebo  | Relative Risk |
| n=161             | n=83                | n=72    |               | n=81                | n=80     |               |
| 55 (34%)          | 5 (6%)              | 5 (7%)  | 0.9           | 29 (36%)            | 11 (14%) | 2.6           |

After consideration of your argument, I agree with your view that the risk of insomnia with HLD200 was overestimated in Study 108 and is an artifact of the study design. It remains possible that the morning release of methylphenidate, which is, after all, the intent of your formulation, could result in early morning insomnia in some patients, such as those who take it very early, but that outcome would have to be weighed against the other effects of the drug.

Regarding your argument that (b) (4) has been demonstrated, as I noted above, a final decision on this issue was not made or included in the CR action taken for this application. I believe this issue will benefit from further consideration during labeling

discussions, (b) (4)  
following resubmission of your application. (b) (4)

I have thus concluded that NDA 209311 for HLD200 (methylphenidate hydrochloride modified release) should be approved for treatment of ADHD, pending agreement on final labeling. I note however, that specific claims beyond general treatment of ADHD, (b) (4) have not yet been decided and will be under consideration during the labeling discussion process. We commit to prompt meetings to discuss labeling following resubmission of your application.

Questions regarding next steps as described in this letter should be directed to Martin Yoon, Regulatory Health Project Manager, Division of Psychiatry Products at (240) 402-3911.

This constitutes the final decision at the Office of Drug Evaluation I level. Any questions concerning your appeal should be addressed to Paul Phillips at (301) 796- 3935.

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.  
Deputy Director (Acting)  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROBERT TEMPLE  
05/21/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 118074

MEETING MINUTES

Ironshore Pharmaceuticals & Development Inc.  
Attention: Margaret J. Sampson, US Agent  
98 San Jacinto Blvd  
Suite 1500  
Austin, TX 78701

Dear Ms. Sampson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Modified-Release Capsules (HLD200).

We also refer to the meeting between representatives of your firm and the FDA on May 5, 2016. The purpose of the meeting was to discuss the clinical, chemistry, manufacturing, and control (CMC), and nonclinical programs supporting the submission of a 505(b)(2) NDA.

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 Shin-Ye Sandy Chang, Regulatory Project Manager at (301) 796-3971, or email [shinye.chang@fda.hhs.gov](mailto:shinye.chang@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
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**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** May 5, 2016, 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:** 118074  
**Product Name:** Methylphenidate Modified-Release Capsules (HLD200)  
**Indication:** Attention Disorder Hyperactivity Disorder  
**Sponsor/Applicant Name:** Ironshore Pharmaceuticals & Development Inc.

**Meeting Chair:** Mitchell Mathis, MD  
**Meeting Recorder:** Shin-Ye Sandy Chang, PharmD

**FDA ATTENDEES**

|                             |                                                      |
|-----------------------------|------------------------------------------------------|
| Mitchell Mathis, MD         | Director, Division of Psychiatry Products (DPP)      |
| Tiffany Farchione, MD       | Deputy Director, DPP                                 |
| Greg Dubitsky, MD           | Clinical Reviewer, DPP                               |
| Ikram Elayan, PhD           | Pharmacology/Toxicology Supervisor, DPP              |
| Hao Zhu, PhD                | Office of Clinical Pharmacology (OCP) Team Leader    |
| Praveen Balimane, PhD       | OCP Reviewer                                         |
| David Claffey, PhD          | CMC Lead, Office of Pharmaceutical Quality (OPQ)     |
| Okpo Eradiri, PhD           | Biopharmaceutics Lead, Division of Biopharmaceutics, |
|                             | Office of New Drug Products (ONDP), OPQ              |
| Rao Kambhampati, PhD        | CMC Reviewer, OPQ                                    |
| Peiling Yang, PhD           | Statistical Team Leader                              |
| Jingling Zhong,, PhD        | Statistical Reviewer                                 |
| Selena Daniels, PharmD, MS  | Clinical Outcome Assessments Staff (COA) Reviewer    |
| Michelle Campbell, PhD      | COA Reviewer                                         |
| Shin-Ye Sandy Chang, PharmD | Regulatory Project manager, DPP                      |

**SPONSOR ATTENDEES**

|                    |                                                                     |
|--------------------|---------------------------------------------------------------------|
| Mr. David Lickrish | President and CEO, Ironshore Pharmaceuticals<br>& Development, Inc. |
|--------------------|---------------------------------------------------------------------|

|                      |                                                                                                                        |
|----------------------|------------------------------------------------------------------------------------------------------------------------|
| Dr. Bev Incledon     | Executive Vice President, Research & Development, Ironshore, Inc.                                                      |
| Dr. Randy Sallee     | Chief Medical Officer, Ironshore Pharmaceuticals & Development, Inc.                                                   |
| Mr. Norberto DeSousa | Vice President, Clinical Operations, Ironshore Pharmaceuticals & Development, Inc.                                     |
| Ms. Jill Kapuscinski | Vice President, Pharmaceutical Operations, Ironshore Pharmaceuticals & Development, Inc.                               |
| (b) (4)              | Regulatory Consultant, (b) (4)                                                                                         |
| Dr. Stephen Faraone  | Distinguished Professor, Psychiatry and Behavioral Sciences, State University of New York - Upstate Medical University |

(b) (4)

## 1.0 BACKGROUND

Methylphenidate hydrochloride modified release capsules (HLD200) are being developed by Ironshore Pharmaceuticals & Development, Inc. (Ironshore) for the treatment of attention deficit hyperactivity disorder (ADHD) in patients age 6 years and older. The Sponsor states that, within each capsule, methylphenidate (MPH) is incorporated into a delayed release (DR) and extended release (ER) coated core that allows for initial release approximately 8 hours after ingestion followed by a controlled rate of release. HLD200 is intended to be taken once daily in the evening and release MPH during the post-awakening period the next day, followed by extended release of MPH throughout the remainder of the day.

The Division of Psychiatry Products (DPP) has met with Ironshore regarding their development program on two previous occasions:

- An End-of-Phase 2 (EOP2) meeting on February 11, 2014, entailed discussion of the preliminary pharmacokinetic (PK) data with this product, the design of a safety and efficacy trial, planned studies (including food effect, dose proportionality, and bioavailability studies), the need to determine partial AUCs in demonstrating bioequivalence, and a requirement for an alcohol dose-dumping study.
- A second EOP2 meeting held on April 2, 2015, involved discussion of the results from a Clinical Endpoint Evaluation Study (HLD200-106). In that trial, the SKAMP-CS (Combined Score) was the primary efficacy endpoint at was to be tested at multiple time points in a prespecified sequence during the day, the first being at 8AM. (b) (4). In addition, the Before School Functioning Questionnaire (BSFQ) during the post-waking hours was a key secondary endpoint (b) (4) (in an April 17, 2014, letter, DPP informed

the sponsor that a submitted manuscript by Faraone and coworkers did support use of the investigator-rated BSFQ as a key efficacy variable in children with ADHD). (b) (4)  
, a separate study of early morning functioning was planned. The design of two key efficacy trials (HLD200-107 and HLD200-108) was discussed. Important points conveyed to the sponsor at this meeting were: (1) the average SKAMP-CS throughout the day was acceptable as a primary endpoint but this scale should be assessed across the entire range of time points at which efficacy was anticipated; (2) a positive result on the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R) AM subscale may be used to replicate early morning efficacy demonstrated on the BSFQ in a second trial provided that it is designated as a key secondary endpoint in the protocol and data to support its validity and reliability in measuring early morning functioning are submitted to the Agency for review and deemed acceptable; (3) a separate safety and efficacy study in adults with ADHD must be conducted to support an indication for patients age 6 years and older unless Ironshore can provide a convincing argument that such a study is unnecessary. Otherwise, a claim for ages 6 to 17 years may be granted (in an April 9, 2014, letter, DPP informed the sponsor that extrapolation of clinical data from children to adolescents was supported by PK data); and (4) approval of an application for HLD200 will carry a postmarketing commitment for a safety and efficacy trial in children 4 to 5 years because there is an apparent need for ADHD medication in this age range.

Clinical studies in the HLD200 development program are summarized in Table 1. All studies are completed except HLD200-108, which is expected to be completed in May 2016. Studies HLD200-107 and HLD200-108 will be the key efficacy trials for the planned NDA.

**Table 1: HLD200 Clinical Studies**

| Study Number                 | Description                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Phase 1 &amp; Phase 2</b> |                                                                                                                                                                                                                                                                                                                                                                |
| HLD200-101                   | Single-dose crossover study comparing the bioavailability of 2 modified-release formulations of HLD200 54mg with MPH IR 20mg in healthy adults.                                                                                                                                                                                                                |
| HLD200-102                   | Single-dose PK study of 2 modified-release formulations of HLD200 54mg in children (ages 6-12) and adolescents (ages 13-17).                                                                                                                                                                                                                                   |
| HLD200-103                   | Single-dose, three-way crossover study of HLD200 100mg in healthy adults. Dosing conditions were fasted, after a high-fat meal, and sprinkled on applesauce.                                                                                                                                                                                                   |
| HLD200-104                   | Two part single-dose study in healthy adults. Part 1 evaluated dose proportionality with HLD200 20mg and 100mg and Part 2 assessed bioavailability after evening HLD200 dosing with a low-fat, low-calorie breakfast.                                                                                                                                          |
| HLD200-109                   | Single-dose, three-way crossover study of a new optimized formulation of HLD200 100mg in healthy adults. Dosing conditions were fasted, after a high-fat meal, and sprinkled on applesauce.                                                                                                                                                                    |
| <b>Phase 3</b>               |                                                                                                                                                                                                                                                                                                                                                                |
| HLD200-106                   | Open-label dose and time optimization for 6 wks followed by a 1-wk randomized, double-blind, placebo-controlled phase with laboratory classroom assessment of efficacy in 43 children (ages 6-12) with ADHD. Evening (9PM $\pm$ 2 hrs) dosing with HLD200 20-100mg. Primary: average SKAMP-CS 8AM-4PM. Key secondary endpoints: BSFQ, SKAMP-CS at 6PM and 8PM. |
| HLD200-107                   | Open-label dose and time optimization for 6 wks followed by a 1-wk randomized, double-blind, placebo-controlled phase with laboratory classroom assessment of efficacy in 155 children (ages 6-12) with ADHD. Evening (8PM $\pm$ 1.5 hrs) dosing with HLD200 20-100mg. Primary endpoint: average SKAMP-CS 8AM-8PM. Key secondary: PREMB-R AM subscale.         |
| HLD200-108                   | Randomized, double-blind, placebo-controlled, parallel group study in children (ages 6-12) with ADHD. Evening (6:30PM-9:30PM) dosing with HLD200 40-80mg x3 wks. Primary endpoint: ADHD-RS-IV total score throughout the day. Key secondary: BSFQ.                                                                                                             |

The Sponsor plans an integrated safety database for the NDA

(b) (4)

(b) (4)

Efficacy data from the two key efficacy trials will not be integrated.

To support use of the PREMB-R AM subscale as the key secondary efficacy endpoint in Study HLD200-107, Faraone and colleagues utilized the data from Study HLD200-106 to assess the reliability and validity of the Daily Parent Rating of Evening and Morning Behavior Scale, Revised (DPREMB-R) morning score and presented the results in an article to be published in the Journal of Attention Disorders (found in Appendix 1 of the Briefing Document). This subscale is comprised of three questions about early morning behaviors that were derived from a survey of expert clinicians. Each item is rated on a 4-point scale (0=none, 1=a little, 2=a moderate amount,, 3=a lot) with the total subscale score ranging from 0 to 12. The questions are:

- (1) How much difficulty did your child have getting up and out of bed this morning?
- (2) How much difficulty did your child have getting ready this morning (e.g., getting washed, dressed, eating breakfast, and getting to school) because of being distracted and inattentive (not because of arguing or refusing to do things)?
- (3) How much was your child arguing or struggling excessively with you this morning?

In that trial, parent/legal guardians were instructed to base their response on the last two school days prior to the site visit. Ratings were reviewed at each visit with the investigator, who then completed the scale based on that two-day interval.

Faraone examined internal consistency reliability using Cronbach's alpha, which was 0.65 with a lower confidence interval boundary of 0.47. Test-retest reliability was modest (Pearson  $r=0.52$ ). Concurrent validity was high with statistically significant correlations with the BSFQ, ADHD-RS, and CGI-Severity scores. Faraone concluded that the morning score of the DPREMB-R is a valid and reliable measure of the effect of ADHD symptoms on morning behavior in children.

Ironshore has requested a preNDA meeting to ensure alignment with DPP on the HLD200 development program and materials to be submitted to support a 505(b)(2) NDA submission.

FDA sent Preliminary Comments to Ironshore on May 2, 2016.

## **2.0 DISCUSSION**

### **2.1. Clinical**

**Question 1:** In the End of Phase 2 (EOP2) meeting minutes dated 15 April 2015, the Agency offered the following statement regarding use of the PREMB-R AM to replicate early morning functioning efficacy:

“The Agency informed the sponsor that a positive finding on the PREMBR morning subscale in trial HLD200-107 may be used to replicate a finding of efficacy based on the BSFQ in trial HLD200-108 provided that 1) Ironshore submits data to support the validity and reliability of the PREMBR morning subscale to measure early morning functioning and 2) this measure is designated as a key secondary endpoint in the protocol for HLD200-107.”

Ironshore is providing the recently published, peer-reviewed manuscript, “Reliability and Validity of the Daily Parent Rating of Evening and Morning Behavior Scale, Revised” (Faraone, Childress, et al., 2015; Appendix 1) as part of the meeting briefing package to support the validity and reliability of the PREMB-R AM to measure early morning functioning. Further discussion of the PREMB-R AM is provided in Section 6.2.2.2.1. The PREMB-R AM has been designated as a key secondary endpoint in the protocol for Study HLD200-107.

**Does the Agency agree that the enclosed publication (Faraone, Childress, et al., 2015) provides the necessary support of the validity and reliability of the PREMB-R AM to measure early morning functioning** (b) (4)  
?

***FDA Response to Question 1:*** We acknowledge the cited supportive literature in the meeting package; however, our assessment is that the evidence of content validity and other measurement properties included in this publication for PREMB-R AM is limited. At this time, we do not have sufficient evidence to determine that the PREMB-R AM is a well-defined and reliable instrument (b) (4). We ask you to submit copies of both the PREMB-R AM and BSFQ, as well as their user manuals for review. If user manuals are not available, then provide details on the instructions and administration of the PREMB-R AM and BSFQ, as well as scoring algorithm and interpretation and missing data plan. In addition, clarify when the instruments were completed and who completed the instruments (parent or clinician). The determination on the acceptability of the PREMB-R AM will depend on the adequacy of submitted data and will be a matter for review.

***Ironshore Response to Preliminary Comments:*** Further discussion is requested. Ironshore would like to gain further understanding around what will be considered sufficient evidence to determine that the PREMB-R-AM is a well-defined and reliable instrument to support labeling claims.

Ironshore believes the following additional data regarding measurement properties of PREMB-R-AM will support the PREMB-R-AM and demonstrate it is a well-defined and reliable instrument (b) (4):

- a) In-depth review of prior literature
- b) Further analysis of data in Faraone et al.
- c) Analyze data from other Ironshore trials.
- d) Attempt to access and analyze data from other researchers to compute reliability and validity statistics.

(b) (4)

Further, the PREMB-R AM is a morning subscale of the PREMB-R or -Parent Rating of Evening and Morning Behavior Scale, Revised, which has an extensive literature in ADHD clinical trials, naturalistic studies, and even a magnetic resonance spectroscopy study. The PREMB-R was first validated and its psychometric properties characterized as a parent-rated measure, with emphasis on total score, which combines morning and evening items. The total score shows good split-half reliability ( $r=0.93$ ), and temporal stability ( $r=0.72$ ), and items are internally consistent as measured by Cronbach's Alpha (0.89). The PREMB-R can also be administered as a clinician rating and has been validated and its psychometric properties characterized when used in this manner. The concurrent validity of the investigator- PREMB-R morning scale is high as measured by its correlations with total ADHD symptoms as measured by the ADHD-RS, overall severity as measured by the CGI-S, and before-school functioning as measured by the BSFQ.

In pivotal trials with HLD200 the PREMB-R-AM was administered by a clinician. At investigator meetings considerable effort and emphasis was made on the training aspects of administration and scoring thru peer education by leading clinical experts in the administration of the PREMB-R and BSFQ as clinician rated instruments.

The validity and measurement properties of the clinician-rated PREMB-R and its subscales, both AM, as well as the clinician rated BSFQ have been detailed in peer reviewed publications.

Does the Agency believe this will be a sufficient body of evidence to confirm reliability and validity?

Ironshore will provide training documentation outlining the use and administration of the scales/sub-scales in the NDA package.

**Discussion:** *The Sponsor clarified that their proposed analyses are intended to further evaluate the measurement properties of the PREMB-R with data on file and/or from other researchers.*

*The Agency reiterated that the publication had limited data on the measurement properties of PREMB-R and confirmed additional evidence is needed to support the adequacy of the instrument (e.g., content validity, reliability, construct validity, ability to detect change, etc.). The Sponsor verbally provided some additional information in regards to the development and validity of the PREMB-R; however, the Agency noted that the Sponsor described face validity rather than content validity, and that the Agency places a greater emphasis on content validity. Content validity refers to the extent that the instrument measures all facets of the measured concept (outcome) that are relevant and important to patients and caregivers (if applicable) and that the items of the instrument are understood and interpreted appropriately. Content validity is established by qualitative research (e.g., literature review, patient/caregiver interviews, expert opinion, etc.). The Agency noted that documentation of content validity is needed.*

*The Agency also asked for clarification about the administration of the PREMB-R. The Sponsor noted that the PREMB-R is usually observer-reported by a parent or caregiver; however, for their clinical trials the PREMB-R was interview-administered by a clinician. The Sponsor agreed to provide information regarding rater training.*

*The Agency encouraged the Sponsor to perform all the supportive analyses as feasible for the PREMB-R (b) (4) as well as for the BSFQ. The key issue is how to determine comparability of the PREMB-R and BSFQ given that these are different instruments and were used separately in each of the pivotal trials. It will be critical for the Sponsor to determine what constitutes a meaningful change or improvement in these scales. This can be evaluated by multiple methods [e.g., review of literature, patient/caregiver input, expert opinion, or anchor-based analyses and cumulative distribution functions (CDFs)]. The Agency recommended that, at minimum, the Sponsor use anchor-based methods and CDF curves to determine responder definitions and clinically meaningful change in instrument scores.*

*To facilitate the assessment of these two instruments, the Agency recommended the Sponsor submit a full evidence dossier in support of the two instruments with the NDA submission (including all evidence to date) for review. The Agency referred the Sponsor to the [Patient Reported Outcomes Guidance](#) to determine what components should be included in the dossier as the Agency would expect the same components for a clinician-reported outcome instrument.*

*The Agency also asked about the specificity of the PREMB-R AM subscale items for ADHD; two items were particularly concerning, 1) difficulty getting out of bed and 2) struggling or arguing in the morning. It seemed that these difficulties could be experienced by many children without ADHD. Dr. Faraone replied that items in this subscale were not intended to be specific for ADHD but instead to speak to the assessment of functioning. The Sponsor agreed to address this concern in their submission of supporting data.*

*At the Sponsor's request, the Agency agreed to try to provide feedback on adequacy of information submitted to support these two instruments by the time of NDA filing.*

**Question 2:** With regard to Ironshore obtaining an indication in adult patients, in the EOP2 meeting minutes dated April 15, 2015, the Agency indicated that it would be "...willing to consider an argument, which you may put forth in your application, that would convince us that a study in adults is unnecessary. If we are convinced, then a claim for the age range you propose (6 years and older) could be approved."

Ironshore intends to seek extrapolation of efficacy from Studies HLD200-107 and HLD200-108 from children to adults (b) (4) (Section 6.2.5). Symptomatic efficacy established in pediatric studies has previously been extrapolated to support adult dosing in other methylphenidate MR products.

**We would like to seek the Agency's feedback on the following question: what is expected to support the extrapolation (b) (4) from children to adults?**

***FDA Response to Question 2:*** (b) (4)

*You might derive some of this evidence from the published literature. The supporting data should be provided in your NDA and will be a matter for review during our examination of your application.*

**Discussion:** *No further discussion.*

***Question 3:*** (b) (4)

Due to the different endpoints and study designs utilized in the pivotal phase 3 studies (HLD200-107 and HLD200-108; [Table 3](#)), efficacy results will not be pooled. Efficacy data will be presented and described in Module 2.7.3.

The plans for the clinical summaries in the NDA are discussed in [Section 6.2.4](#).

**Does the Agency agree with the proposed data integration and pooling strategy and that no additional pooled analyses are needed to support the NDA?**

***FDA Response to Question 3: No.*** (b) (4)

**Discussion:** *No further discussion.*

**Question 4:** Regarding the number of clinical studies and the differences between study designs, Ironshore proposes summarizing clinical data in Modules 2.7.4 Summary of Clinical Safety (including an integrated analysis of safety) and 2.7.3 Summary of Clinical Efficacy rather than in Module 5.3.5.3 ISS and Integrated Summary of Efficacy, respectively ([Section 6.2.4](#)).

**Does the Agency agree that the HLD200 NDA can be submitted without integrated clinical summaries in Module 5.3.5.3?**

**FDA Response to Question 4:** *Yes, we agree that an ISS and ISE are not necessary.*

**Discussion:** *No further discussion.*

**Question 5:** Risk mitigation plans for HLD-200 are discussed in [Section 6.2.6](#). Ironshore will provide a medication guide in the NDA submission.

**Does the Agency agree that no risk evaluation and mitigation strategy (REMS) or any other REMS elements beyond the medication guide are required for the HLD200 NDA submission?**

**FDA Response to Question 5:** *It seems unlikely that a REMS or other REMS elements beyond the medication guide will be required, but the need for a REMS will be a matter for review.*

**Discussion:** *No further discussion.*

**Question 6:** All Ironshore HLD200 clinical studies, including post-treatment follow up, will be completed at the time of NDA submission and will be included as part of the submission ([Section 6.2.1](#)). Accordingly, Ironshore does not plan to submit a safety update report 120 days following NDA submission.

**Does the Agency agree that no safety update report is required to be submitted 120 days following NDA submission?**

**FDA Response to Question 6:** *Yes, we agree that a 120-Day Safety Update Report is not necessary.*

**Discussion:** *No further discussion.*

## **2.2. Chemistry, Manufacturing, and Controls**

**Question 7:** Ironshore has performed in vitro dose-dumping studies with HLD200, which demonstrated no release of methylphenidate at ethanol concentrations up to and including 20% in the media ([Section 6.3.2.4](#)). At 40% ethanol concentrations, no early release was observed in the first 30 minutes, an average of 10% of methylphenidate was released in 45 minutes, up to 50% methylphenidate was released after 60 minutes, and approximately 96% methylphenidate was released after two hours. Ironshore will include these results in the NDA. It is unlikely that a sustained (two hour) alcohol concentration of 40% could be achieved in vivo, and at concentrations up to 20% alcohol no release was observed in vitro. In a worst-case scenario where a patient took a 100 mg HLD200 capsule concomitantly with a 40% in vivo level of alcohol, that patient would effectively be dosed 100 mg of methylphenidate over a 2-hour period; that is, the in vivo concentration would be less than that after 100 mg IR methylphenidate. Concerta was studied at doses of up to 144 mg without

important AEs; therefore, Ironshore believes that dose dumping in the presence of alcohol is adequately addressed and any potential in vivo exposures in the presence of alcohol will be within the known safe methylphenidate exposures.

**Based on these results, Ironshore does not believe an in vivo alcohol study is needed. Does the Agency agree?**

***FDA Response to Question 7:*** Based on the information provided in the briefing package, the potential for alcohol dose dumping for your proposed drug product seem to have been adequately investigated. We agree that an in vivo alcohol study is not needed; however, summarize the results of the in vitro alcohol dose-dumping studies in the proposed labeling.

***Discussion:*** No further discussion.

***Question 8:*** HLD200 is comprised of a coated core which is encapsulated into five strengths (20, 40, 60, 80, and 100 mg) varying only in (b) (4), capsule color, and size. A total of 15 encapsulated lots (three batches of each strength from five coated core batches) are currently on stability.

**Part 1: Does the Agency agree to the proposed stability strategy (Section 6.3.2.5) that includes:**

**40 mg, 60 mg, 80 mg, 100mg**

- 2 batches of each strength with 12-month long-term data and 6-month accelerated data at the time of initial NDA submission
- 1 batch of each strength with 9-month long-term data and 6-month accelerated data at the time of initial NDA submission; submission of 12-month long-term data for each strength within 30 days of initial NDA submission

**20 mg**



***FDA Response to Question 8.1:*** We agree with your proposal for submitting the stability data for the 40 mg, 60 mg, 80 mg, and 100 mg strength capsules but, for the 20 mg strength capsules, we recommend you to submit the updated stability data during the review cycle.

***Ironshore Response to Preliminary Comments:*** The timeline for submission of outstanding stability data of 20 mg capsule batches to the NDA is provided below.

| Batch Number | Dose Strength | Duration of Stability | NDA Amendment Submission Date | Time from Submission of Original NDA* |
|--------------|---------------|-----------------------|-------------------------------|---------------------------------------|
| 4792         | 20 mg         | 12 months             | 21-Sep-2016                   | 2 months                              |
| 5046         | 20 mg         | 12 months             | 13-Jan-2017                   | 5 months                              |

\*The original NDA submission is planned for 19-Aug-2016 and will include 12 months stability of 1 batch of 20 mg HLD200 (batch 4021) and 3 batches of 40, 60, 80, and 100 mg HLD200 (batches 4021, 4683, and 4684).

Does the Agency agree that submission of this additional stability data within this timeframe from initial NDA submission will not delay the PDUFA timeline for review of the NDA?

**Discussion:** *This is acceptable.*

**Part 2: Does the Agency agree to the use of the long-term stability data on the 40 mg, 60 mg, 80 mg, and 100 mg capsules as outlined in Part 1 for establishment of the expiration date for the 20 mg capsule?**

**FDA Response to Question 8.2:** *Establishment of the expiration date is a review issue that would be based on the data provided for all the strengths including the updated data provided for the 20 mg strength capsules.*

**Discussion:** *No further discussion.*

## 2.3. Nonclinical

**Question 9:** Ironshore has not conducted any nonclinical studies to support the safety of HLD200. Ironshore will rely on the following nonclinical information to support the safety of methylphenidate and marketing authorization of HLD200:

- 1) FDA's findings of the safety of methylphenidate as reported in label of the reference listed drug (RLD), Ritalin<sup>®</sup> (Section 6.4.1);
- 2) A summary of the nonclinical literature supporting the safety of methylphenidate for clinical use, provided in the Investigator Brochure (Version 03, 02 JUN 2015) of the initial IND submitted by Ironshore (Section 6.4.2); and
- 3) An update to the summary of the nonclinical literature to identify any potential omissions in the previous summary and any new (2011-present; search performed 01-07 March 2016), publically available information relevant to the safe use of methylphenidate in ADHD patients (Section 6.4.3).

Ironshore believes that the nonclinical information provided by these 3 components and clinical studies conducted with HLD200 is sufficient to support the safety of methylphenidate and the marketing authorization of HLD200 for the treatment of ADHD. Ironshore plans to summarize the nonclinical information in Module 2.4 of the NDA. Ironshore does not intend to provide nonclinical summaries in Module 2.6.

**Does the Agency agree with this approach and that this information will be sufficient to support the safety and marketing authorization of HLD200 for the treatment of ADHD?**

**FDA Response to Question 9:** *On face, we agree with your approach, unless there are impurities, degradants, or excipients in your product that would require qualification.*

**Ironshore Response to Preliminary Comments:** There are no impurities, degradants, or excipients in the HLD200 drug product that require qualification based on the body of data generated.

**Discussion:** *The Agency acknowledged Sponsor's response, and will review the data once it is submitted.*

#### 2.4. Additional Biopharmaceutics Comment

Refer to the "Study May Proceed" letter dated 4/24/2013 for the general biopharmaceutics advice on dissolution method development, setting of dissolution acceptance criteria, justification of the extended release claim and details on the in vitro alcohol dose dumping experiments.

**Discussion:** *No further discussion.*

#### 2.5. Additional Clinical Pharmacology comments

- *Please confirm that a relative bioavailability study with the "to-be-marketed" formulation compared to a reference listed drug has been conducted.*

**Ironshore Response to Preliminary Comments:** Further clarification is requested.

Ironshore has characterized HLD200 (previous manufacturing process formulation) and Ritalin in Study HLD200-101. The PK of the commercial formulation is evaluated in Study HLD200-104 and HLD200-109. Although the formulations were manufactured at different facilities, (b) (4)

(b) (4) The difference between formulations is confined to (b) (4), with the commercial formulation manufactured using (b) (4) process as opposed to the (b) (4) process previously employed. The commercial formulation is very similar to the previous formulation based on a comparison of in vitro and in vivo

performance, hence no further characterization of PK for the commercial formulation is deemed necessary. Ironshore and FDA agreed on this approach during EOP2 date April 2, 2015 and the following correspondence provided: EOP2 April 2, 2015 Meeting Discussion, EOP2 Meeting Minutes (received April 15, 2015), FDA Response provided in General Correspondence (email dated March 30, 2015).

**Discussion:** *Because the manufacturing site and the manufacturing process were different for the old formulation compared to the new formulation, this constitutes a Level 3 per SUPAC-MR guidance. The in vitro bridging between the old and new formulations has not been established. The Sponsor proposed* (b) (4)

**Post-meeting comment:** *The Agency disagreed with this approach, especially given that the proposed drug product has a very complex release mechanism. Therefore, the Agency recommends that the Sponsor conduct a relative bioavailability study bridging the to-be-marketed formulation to the RLD.*

- *Please confirm that the formulation used in the key clinical studies (pivotal efficacy, BA study, dose-proportionality, food-effect study etc.) is identical to the “to-be-marketed” formulation.*

**Ironshore Response to Preliminary Comments:** Yes, the formulation used in key clinical studies is identical to the “to-be-marketed” formulation.

**Discussion:** *No further discussion.*

- *Please confirm that an appropriate food-effect study has been conducted as per the previous discussion/feed-back with the Agency. If any deviations were performed in the clinical study, adequate supporting rationale to justify the deviations should be provided at the time of the submission.*

**Ironshore Response to Preliminary Comments:** Confirmed, the Agency’s feed-back has been incorporated into the study design and execution of the food-effect study. Any deviations and supporting rationale will be included in the NDA.

**Discussion:** *The Agency requested that the Sponsor ensure all the details and relevant data pertaining to food-effect will be included in the NDA submission along with detailed analyses.*

- *Please provide plans to address in the label the following scenarios: (1) concomitant administration of gastric pH modulating products (e.g., proton-pump inhibitors etc.) (2) patients with any scenarios leading to changed/different GI motility (3) any other scenarios (for e.g., concomitant night-time dosing of Intuniv or Kapvay as adjunctive*

*with stimulants for ADHD etc.) that can alter the unique drug absorption/release feature of the product.*

*Please plan to include all supporting information (e.g., scanning or scintigraphy data, literature data, or any other relevant information regarding delayed release of methylphenidate) on mechanisms/location of drug release from the proposed formulation and potential impact of bowel movement (e.g., diarrhea or constipation) and gastric pH changes, and any GI disease conditions on drug release in your clinical pharmacology summary in the NDA package.*

**Ironshore Response to Preliminary Comments:** Ironshore does not believe that additional clinical pharmacology studies to investigate administration with gastric pH modulating products, subjects with altered GI motility or concomitant administration with Intuniv or Kapvay are necessary. Owing to the unique characteristics of HLD200 which result in the release of methylphenidate from the formulation being a function of both pH and GI residence time it is not expected that alterations of GI motility or pH modulating agents would have a significant impact on the release characteristics. To date, in our clinical experience, we have observed low levels of pharmacokinetic variability and concomitant low levels of variability with respect to efficacy across a broad range of patients. Studies have included patients with constipation, diarrhea and in one case, a subject with surgical removal of the ileum.

Ironshore intends to provide a literature-based argument in the NDA that demonstrates the highly extended lag period preceding drug release from the formulation ensures the product is present in the terminal small bowel or proximal large bowel at the time of initial drug release. Even in the event of a predominantly diarrhea state (IBS-D for example) where subjects may experience a rapid upper GI transit time the overall transit time or colonic transit time is within normal ranges. In the event of a constipated state the product is resident in the large bowel for more than sufficient time for 100% drug absorption to occur and similarly the onset of drug release would be within the terminal small bowel or proximal large intestine as constipation normally would manifest as a result of prolonged colonic transit time with normal small bowel transit times. Concerning the concomitant use of gastric pH modifying agents, a typical literature value for the average increased gastric pH is approximately 4.5 – 5.0. The pH component of HLD200 is insoluble at pH less than 7.0 furthermore the (b) (4) the HLD200 delayed release (DR) layer ensure that there is a delay in the wetting of the coating further delaying the dissolution even at pH near or greater than pH 7.0. Thus even at significantly elevated gastric pH for a short period of time prior to gastric emptying, no drug release would be expected. Lastly, with respect to concomitant use with other drugs which may have direct effect on gastric or intestinal motility, such as Intuniv, for the reason above concerning diarrhea or constipation a similar effect on HLD200 release and absorption would be expected.

**Discussion:** *The Sponsor confirmed that they will provide a comprehensive body of data (including relevant literature, information from their clinical PK studies, and any other supporting information) in the NDA package to address the impact of pH, gut motility, and concomitant medicines on the products clinical PK. The Agency requested that the Sponsor ensure concise summaries and underlying rationale for these extrinsic effects are clearly*

*articulated in their clinical pharmacology summary. The Agency stated that based on our independent assessment of the Sponsor's information and rationales, additional clinical studies (post-approval) may still be required.*

### **3.0 PREA REQUIREMENTS**

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

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

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](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **4.0 PRESCRIBING INFORMATION**

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

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

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

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

## **5.0 SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

## **6.0 505(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.

|                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>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</b></p> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| <b>Source of information<br/>(e.g., published literature, name of<br/>listed drug)</b> | <b>Information Provided<br/>(e.g., specific sections of the 505(b)(2)<br/>application or labeling)</b> |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>1. Example: Published literature</i>                                                | <i>Nonclinical toxicology</i>                                                                          |
| <i>2. Example: NDA XXXXXX<br/>“TRADENAME”</i>                                          | <i>Previous finding of effectiveness for<br/>indication X</i>                                          |
| <i>3. Example: NDA YYYYYY<br/>“TRADENAME”</i>                                          | <i>Previous finding of safety for<br/>Carcinogenicity, labeling section XXX</i>                        |
| <i>4.</i>                                                                              |                                                                                                        |

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.

## **7.0 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).

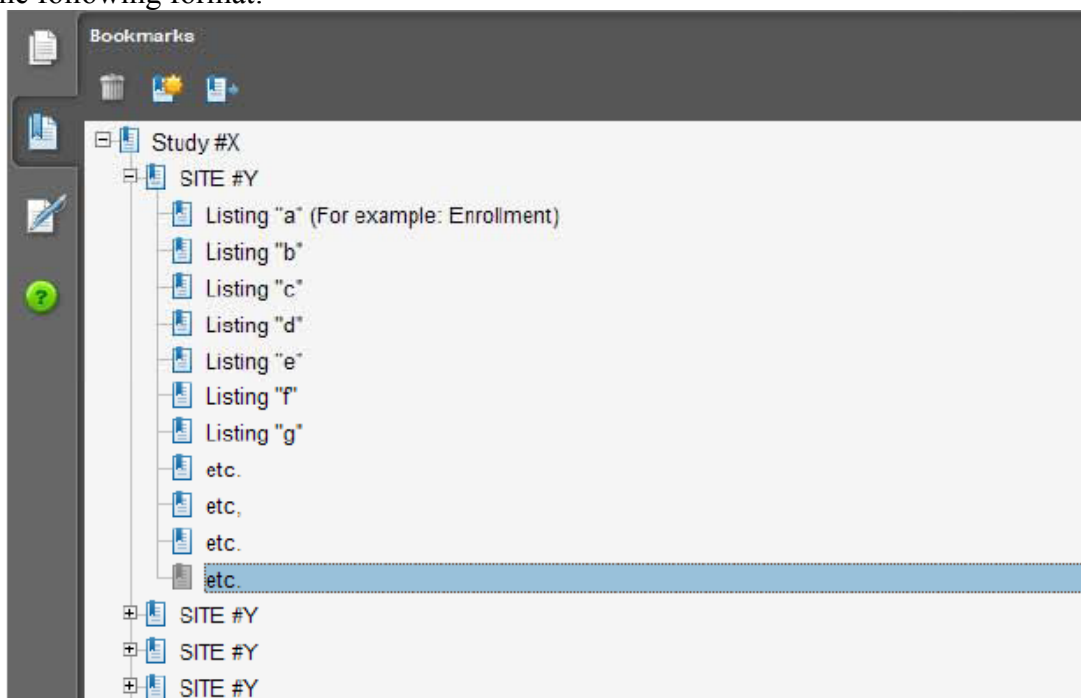
### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

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 <sup>1</sup> | 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:



<sup>1</sup> 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](mailto:ESUB@fda.hhs.gov)

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05/27/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 118074

MEETING MINUTES

Ironshore Pharmaceuticals & Development Inc.  
Attention: Margaret J. Sampson, US Agent  
Partner, Vinson & Elkins LLP  
2801 Via Fortuna  
Suite 100  
Austin, TX 78746-7568

Dear Ms. Sampson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate HCl (b) (4)mg Modified-Release Capsules.

We also refer to the meeting between representatives of your firm and the FDA on April 2, 2015. The purpose of the meeting was to discuss your Phase 3 clinical development program, (b) (4)

(b) (4) and (b) (4) a study examining the pharmacokinetic effects (PK) of HLD200 in a food effect study.

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 Shin-Ye Sandy Chang, Regulatory Project Manager  
[shinye.chang@fda.hhs.gov](mailto:shinye.chang@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D  
CAPT, USPHS  
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**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End of Phase 2  
**Meeting Date and Time:** April 2, 2015 10:00 –11:00 AM  
**Meeting Location:** 10903 New Hampshire Ave.  
White Oak Campus, Bldg 22, Rm 1421  
Silver Spring, MD 20993-0002

**Application Number:** 118074  
**Product Name:** Methylphenidate HCl Modified-Release Capsules.  
**Indication:** Attention Deficit and Hyperactivity Disorder  
**Sponsor/Applicant Name:** Ironshore Pharmaceuticals & Development Inc.

**Meeting Chair:** Mitchell Mathis, M.D.  
**Meeting Recorder:** Shin-Ye Sandy Chang, Pharm.D.

**FDA ATTENDEES**

Mitchell Mathis, M.D., Division Director  
Tiffany Farchione, M.D., Division Deputy Director  
Jing Zhang, M.D., Clinical Team Leader  
Greg Dubitsky, M.D., Clinical Reviewer  
Hao Zhu, Ph.D., Clinical Pharmacology Team Leader  
Praveen Balimane, Ph.D., Clinical Pharmacology Reviewer  
Jinglin Zhong, Ph.D., Statistics Reviewer  
Shin-Ye Sandy Chang, Pharm.D., Senior Regulatory Project Manager

**SPONSOR ATTENDEES**

Dr. Bev Incledon, Senior VP Research & Development  
Dr. Randy Sallee, Chief Medical Officer  
Mr. David Lickrish, President and CEO

(b) (4)

Ms. Jill Kapuscinski, Program Manager

## 1.0 BACKGROUND

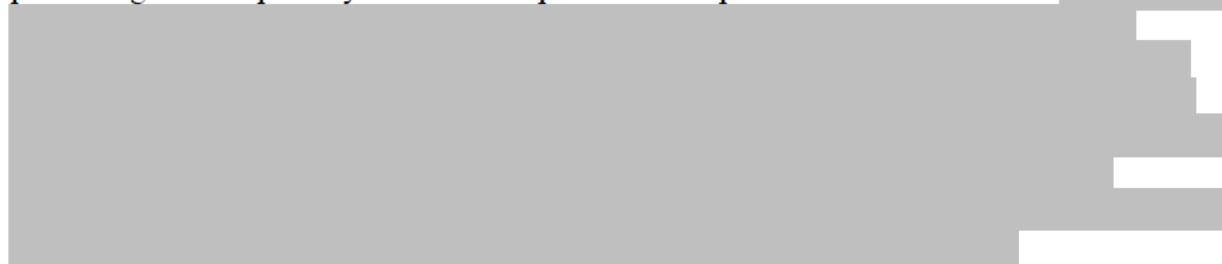
Ironshore developed HLD200 (Methylphenidate Modified Release capsules) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The HLD200 capsule is comprised of a central core of methylphenidate (MPH) coated with an extended release film coating and an external delayed release coating. The dual coatings are designed for the release of MPH at a controlled rate following an initial delay of approximately 8 hours. The release profile of HLD200 is expected to allow for once-daily evening dosing and to provide relief of ADHD symptoms from the time of waking the next morning throughout the remainder of the day.

Thus far, the following studies in the HLD200 development program have been completed:

- HLD200-101: comparative bioavailability study in 12 healthy adults with two MPH HCl Modified Release 54mg formulations and an Immediate Release MPH HCl marketed formulation.
- HLD200-102: adaptive design study comparing the pharmacokinetics (PK) of up to two HLD200 formulations (54mg) given in the evening in pediatric patients with ADHD.
- HLD200-103: comparative PK study of HLD200 100mg under fasted, fed, and sprinkled state in healthy adults. (Tmax in the fed state was about 3 hours longer than in the fasted or sprinkled-on-food states.)
- HLD200-106: Phase 3 Clinical Endpoint Evaluation Study (CEES) of HLD200 in 43 pediatric patients with ADHD. This trial is further described below.

### HLD200-106

Study HLD200-106 consisted of a 6-week open-label dose- and time-optimization phase, followed by a one-week double-blind, placebo-controlled, parallel-group phase. Doses were optimized in the range of 20mg to 100mg daily in the evening. At the end of the double-blind treatment period, the treatment effects were assessed over the course of a day in a laboratory classroom setting. The statistical analysis plan contained in the April 16, 2014, version of the study protocol specified that the primary efficacy measure was the SKAMP-CS (Combined Score) tested at multiple time points between 8AM and 4PM in the following order, with termination of testing when a non-significant result ( $p > 0.05$ ) was observed: 8AM, 9AM, 10AM, 12PM, 2PM, and 4PM. Key secondary endpoints were the SKAMP-C at 6PM, the SKAMP-C at 8PM, and the BSFQ (Before School Functioning Questionnaire) in the morning, in that order and presuming that the primary measure was positive at all points from 8AM to 4PM. (b) (4)



(b) (4)



Based on a comparison of PK data across children, adolescents, and adults, the Agency informed the sponsor in an April 9, 2014, letter that data from children could be extrapolated to adolescents but not to adults. A claim for ADHD in adult patients would require separate safety and efficacy studies because the use of MPH in adults may be accompanied by safety concerns that are not as relevant for pediatric population.

To complete the development program, Ironshore plans to conduct 4 additional studies:

- HLD200-104: PK profile and dose proportionality study in 48 healthy subjects.
- HLD200-109: comparative PK study of HLD200 100mg under fasted, fed, and sprinkled state in healthy adults to evaluate a recent modification to the manufacturing process for HLD200.
- HLD200-107: pivotal safety and efficacy trial in children ages 6-12 with ADHD years in a laboratory classroom setting.
- HLD200-108: safety and efficacy trial in children ages 6-12 with ADHD years to assess early morning functioning.

Trials HLD200-107 and HLD200-108 are described in more detail below.

#### HLD200-107

After screening and washout of prior ADHD medication, this trial will consist of a 6-week open-label treatment optimization phase followed by a one-week randomized, double-blind, placebo-controlled treatment phase, ending with a one-day laboratory classroom assessment.

The sponsor intends to randomize 120 patients, ages 6 to 12 years at screening, with a DSM-5 diagnosis of ADHD, as confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). Patients must also have an ADHD-RS-IV total score must be  $\geq 26$  and, at screening or baseline, be at or above the 90<sup>th</sup> percentile normalized for sex and age in at least one of the following categories of the ADHD-RS-IV: Hyperactive-Impulse, Inattentive, or Total Score. A patient's CGI-Severity score must be  $\geq 4$  with a CGI-P<sup>1</sup> score  $\geq 10$  at screening or baseline to be eligible for inclusion. Parents or legal guardians must confirm the presence of before-school impairment in functioning and difficulties performing the morning routine. Patients with a cardiac condition that increases their vulnerability to sympathomimetic effects, history of a seizure disorder, Tourette's disorder, alcohol abuse, or illicit drug use; history of no response or intolerance to MPH, or active suicidal ideation (among other things) will be excluded.

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<sup>1</sup> CGI-P = Conners Global Index-Parent version.

At the start of the optimization phase, patients will take HLD200 20mg or 40mg (depending on prior treatment) for one week with an additional 4 weekly visits for treatment adjustment to achieve both an optimal dose and an optimal drug administration time prior to the randomized phase. The dose may be adjusted in 20mg to 40mg increments, with a maximum dose of 100 mg/day and/or 3.7 mg/kg, whichever is achieved first.<sup>2</sup> Optimal treatment is defined as one that is safe and well tolerated and produces a minimum improvement from baseline of at least 33% for each of 3 scales (ADHD-RS-IV, BSFQ, and CGI-P). At the same time, time adjustments for taking study drug may be made in increments of 30 to 60 minutes within the interval of 6:30PM to 9:30PM (but with dosing at least one hour after dinner). Also, there must be a difference of less than 10 points in the BSFQ between the last 2 visits of the optimization phase.

At the beginning of the randomized phase, patients will be assigned (in a 1:1 ratio) to double-blind treatment with either HLD200 or placebo for 7 evenings. Patients will receive study drug at their optimal dose and treatment time. Prior to randomization, patients will undergo an abbreviated practice laboratory school day for acclimatization to the timing and procedures of the classroom setting. One week later (the morning after the 7<sup>th</sup> double-blind evening dose), patients will return for assessments in the laboratory classroom from 8AM to 8PM.

The primary efficacy endpoint will be the model-adjusted average of all SKAMP-CS assessments during the classroom day from 8AM to (b) (4). The difference between HLD200 and placebo will be tested at an alpha level of 0.05 using MMRM (Mixed Model Repeated Measures). If the primary outcome shows statistical superiority of HLD200 over placebo ( $p < 0.05$ ), an assessment of onset and duration of efficacy will be conducted using a fixed sequence testing procedure. Time points will be tested using a model-based t-test procedure in the following order: (b) (4)

The onset time will be claimed at the earliest time point at which the drug/placebo difference is statistically significant ( $p < 0.05$ ). The duration of efficacy will be the difference between the onset time and the latest consecutive time point at which the difference between the treatments is still statistically significant ( $p < 0.05$ ).

No key secondary endpoints are specified.

General secondary endpoints include the following (b) (4)  
(b) (4) SKAMP-CS, PERMP- (b) (4)

Safety endpoints include vital signs, 12-lead ECGs, height and weight, and C-SSRS (Columbia-Suicide Severity Rating Scale). At each visit, the investigator will directly question the patient and/or parent/legal guardian about any problems related to sleep and, if sleep problems are present, will follow-up with questions regarding sleep onset, quality, and quantity.

<sup>2</sup> A maximum dose of 3.7 mg/kg places a limit on dosing for patients under 27 kg (59 pounds), who will receive a maximum dose under 100mg. PK data suggest that exposure is dependent on dose and body weight and independent of age.

<sup>3</sup> PERMP = Permanent Product Measure of Performance.

### HLD200-108

This will be a randomized, double-blind, placebo-controlled, parallel group trial

(b) (4)

in children (ages 6-12 years) with ADHD.

(b) (4)

A total of 180 patients will be enrolled from 16 to 20 sites. Patients must be 6 to 12 years of age at screening and have a DSM-5 diagnosis of ADHD, confirmed with the MINI-KID. Patients must have demonstrated an adequate clinical response to MPH. The ADHD-RS-IV total score must be  $\geq 26$  and, at screening or baseline, be at or above the 90<sup>th</sup> percentile normalized for sex and age. The CGI-Severity score must be  $\geq 4$  with a CGI-P score  $\geq 10$  at screening or baseline. A parent or legal guardian must confirm the presence of before-school impairment in functioning and difficulties performing a morning routine of at least 30 minutes. Body weight must be at least 20 kg. Otherwise, inclusion and exclusion criteria are similar to those for trial HLD200-107.

After screening and washout, patients will be randomized in a 1:1 ratio to HLD200 or placebo for 3 weeks of treatment. Dosing will begin at 40mg each evening with a dose increase to 60mg after one week and an increase to 80mg (and/or a dose not to exceed 3.7 mg/kg) after the second week. After dose escalation above 40mg, subjects will be allowed to reduce their dose one level (i.e., from 60mg to 40mg or from 80mg to 60mg) if needed for tolerability. (Telephonic contact will be made during the third week of treatment to determine if a decrease in dose is indicated prior to the final visit.) Patients who cannot tolerate the 40mg dose will be dropped from the study. Thus, during the third week, patients will receive 80mg or their maximally tolerated dose each evening. In addition to adjusting the dose, the timing of the evening dosing may be adjusted in 30 to 60 minute increments each week to achieve optimal morning control of ADHD symptoms (within the window of 6:30PM to 9:30PM). Patients should not consume food within 2 hours prior to taking their dose of study drug and should not eat after dosing until the following morning.

(b) (4)

. The differences between HLD200 and placebo will be tested at a two-sided alpha level of 0.05 and will be analyzed using MMRM at the end of the third week of treatment.

Safety endpoints include vital signs, clinical laboratory tests, height and weight, and C-SSRS. At each visit, the investigator will directly question the patient and/or parent/legal guardian about any problems related to sleep and, if sleep problems are present, will follow-up with questions regarding sleep onset, quality, and quantity.

Following completion of the above studies, Ironshore plans to submit a 505(b)(2) NDA for the use of HLD200 in the treatment of ADHD in patients age 6 years and older.

The sponsor has requested an End-Of-Phase 2 meeting to address the following objectives:

- 1) Seek agreement on the design of the two Phase 3 clinical studies required to support a 505(b)(2) NDA submission.
- 2) Ensure that the HLD200 clinical trial program as described in Section 6 will provide the comprehensive data package required to support approval of a 505(b)(2) NDA.
- 3) Ensure that the clinical trial data generated from both Phase 3 studies, if successful, will be included in the FDA-approved labeling for HLD200, specifically with regard to the reporting of positive outcomes on the Before School Functioning Questionnaire (BSFQ) investigator-rated measures of early-morning ADHD symptoms and functioning before school.

FDA sent Preliminary Comments to Ironshore Pharmaceuticals & Development Inc. on March 3, 2015.

## **2.0 DISCUSSION**

### **2.1. Clinical**

#### **Pivotal Efficacy Study**

**Question 1:** Study HLD200-107 will be a phase 3, outpatient, multicenter (United States sites), optimized-dose, forced-withdrawal, randomized, double-blind, placebo-controlled, 2-arm parallel-design laboratory classroom study of HLD200 in 150 children (aged 6-12 years) diagnosed with ADHD enrolled to achieve 120 completers. The total duration of this trial will be up to 11 weeks and include 3 distinct phases, including: a) up to 4 weeks of screening; b) 6 weeks of open-label, flexible dose/time optimization; and c) 1 week of randomized, double-blind HLD200 (20, 40, 60, 80, or 100 mg optimal treatment) or placebo treatment, at the conclusion of which testing will be conducted in a laboratory classroom setting using the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) measure.

***Ironshore believes that the current study design, summarized above, will be sufficient to demonstrate efficacy to support approval of a 505(b)(2) NDA application. After review of the complete draft protocol provided in Appendix A in this EOP2 Meeting Package, does the FDA agree?***

#### **Preliminary Comments:**

*We have the following comments regarding Trial HLD200-107:*

- 1) *Designation of the average SKAMP-CS throughout the day as the primary efficacy measure is acceptable. However, the range of time points should encompass both the expected time of therapeutic onset and expected duration of effect, as defined in the protocol. Thus, if you expect the duration of effect to extend until 6PM, for example, the SKAMP-CS at this time point should be included in the average.*

**Sponsor Response:** Agree.

- 2) *Statistical testing of the difference between the HLD200 and placebo group on the SKAMP-CS should be conducted at each time point in the range, at a nominal alpha level of 0.05, to demonstrate time of effect onset and duration of efficacy. However, because these results will not be part of formal hypothesis testing to ascertain efficacy in ADHD, it is unnecessary to pre-specify the order of testing of these time points.*

**Sponsor Response:** Agree.

Assuming success on the primary efficacy endpoint, Ironshore plans to include a plot of SKAMP-CS statistical model results by time point and treatment group on the laboratory classroom day in the HLD200 label. In response to Question 1, the Agency outlined an approach for conducting statistical testing of the difference between HLD200 and placebo at each time point at a nominal alpha level of 0.05 with no pre-specified order of testing of time points. Please confirm that the Agency's suggested approach will permit Ironshore to include a SKAMP-CS time point by treatment group plot in the HLD200 label.

**Post-meeting Comment:** *The requirement we previously imposed (pre-specifying a fixed-sequence testing procedure) for the claim of onset time and duration of efficacy was re-visited. The review team concluded that if the primary endpoint was the average score throughout the laboratory classroom day, then there is no need to pre-specify a fixed-sequence for comparing the efficacy at individual time points. If the trial supports efficacy, the time course of plot throughout the laboratory classroom day will be included in the labeling.*

3)

(b) (4)

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(b) (4)

- 4) *Please resolve the discrepancy in dosing relative to the time of food intake for this trial:* (b) (4)

**Sponsor Response:** Protocol will be revised accordingly.

**Discussion:** Ironshore reviewed the results of trial HLD200-106 as well as their rationale for planning to conduct two separate pivotal efficacy trials (HLD200-107 and HLD200-108), as described above. (b) (4)

#### **Post-waking, Early Morning Function Evaluation Study**

**Question 2:** Study HLD200-108 will be a phase 3, outpatient, multicenter (United States sites), randomized, double blind, placebo-controlled, forced/flexible-dose/time, 2-arm parallel-design study of HLD200 in 180 children (aged 6-12 years) diagnosed with ADHD enrolled to achieve 140 completers. The total duration of this trial will be up to 7 weeks with 2 distinct phases, including a) up to 4 weeks of screening and b) 3 weeks of randomized, double-blind HLD200 or placebo treatment utilizing a forced/flexible-dose/time regimen. During this latter phase, subjects will begin dosing at 40 mg with forced titration to 60 mg and 80 mg over the subsequent two weeks, respectively. Subjects will be permitted to reduce dose by one step (20 mg) before settling on their final dose, to be administered until the end of the third week. (b) (4)

*Ironshore believes that the current study design, summarized above and described in detail in the draft protocol provided in Appendix B in this EOP2 Meeting Package, will be sufficient to assess HLD200's ability to improve symptoms and functioning of ADHD subjects during their post-waking, early-morning routine,* (b) (4)

*As previously agreed, if this result is demonstrated in the study data, Ironshore intends to incorporate wording to this effect in the Clinical Studies Section*

**(Section 14; 21 CFR201.56(d) and 201.57) of the package insert accompanying HLD200's NDA submission. Does the FDA agree?**

**Preliminary Comments:** The proposed endpoint model (b) (4) is not acceptable. The endpoint model for this trial should consist of the ADHD-RS-IV total score as the primary efficacy measure and the clinician-rated BSFQ total score as the key secondary measure. We feel that it is critical that this trial demonstrate efficacy in treating ADHD throughout the day. If this is demonstrated, then findings on the BSFQ may be tested. Positive results on the BSFQ can provide partial evidence to support labeling of an effect on symptoms in the before-school timeframe. However, as noted above, this result will need to be replicated before the claim can be permitted in labeling.

**Sponsor Response:** Agree. The endpoint model for HLD200-108 study will consist of the ADHD-RS-IV total score as the primary efficacy measure and the clinician-rated BSFQ total score as the key secondary measure.

Regarding replication of the BSFQ, Ironshore believes that our program is similar to other programs that combine a laboratory classroom study using more pure efficacy measures, like SKAMP, with outpatient studies using a hybrid efficacy/functional measure, such as ADHD-RS, or in our case, BSFQ and ADHD-RS. Programs using an outpatient study to extend the efficacy claim into the early evening by extending the time period of assessment have not been asked to replicate; therefore, it is not clear to Ironshore why there is a request to replicate a demonstration that our product also has similar efficacy from the time of waking. This is not a new domain of symptoms and function, but rather, an extended time period of efficacy assessment.

**Discussion:** The need to replicate a positive efficacy finding on early morning functioning from trial HLD200-108 was discussed in view of the fact that this is a novel claim for an ADHD medication. In particular, the Agency expressed concern that three sources of potential variability might adversely affect the early morning clinical effectiveness of this product: 1) timing of the evening dose, 2) release time of drug the following morning, and 3) the rate of release in the morning. For these reasons, the Agency will require replication to support a claim for early morning functioning in future labeling. Regarding the timing of evening dosing, Ironshore explained that they have found that the dosing window seems to be wider than originally thought because of the lack of sleep-related side effects. Also, this product was carefully designed to insure early morning release and an appropriate release rate to produce an effect both early in the morning and throughout the day. Although these considerations were somewhat reassuring to the Agency, it was still felt that replication of efficacy on early morning functioning was necessary. The Agency informed the sponsor that a positive finding on the PREMBR morning subscale in trial HLD200-107 may be used to replicate a finding of efficacy based on the BSFQ in trial HLD200-108 provided that 1) Ironshore submits data to support the validity and reliability of the PREMBR morning subscale to measure early morning functioning and 2) this measure is designated as a key secondary endpoint

*in the protocol for HLD200-107. The sponsor also intends to assess the PREMBR in trial HLD200-108, which is acceptable to the Agency.*

***Agency comments on PK characterization:*** *Keeping in mind the novelty of the formulation (i.e., prolonged delay time, the agency is concerned about the intra- and inter-subject variability that can impact the overall safe and effective use in children. The sponsor is requested to fully characterize the intra-subject and inter-subject variability of two unique PK characteristics: 1) the time interval with no meaningful drug release, and 2) the early exposure. We suggested that the time interval with no meaningful drug release be calculated from the time of dosing to the time when a threshold concentration is achieved. The threshold concentration is defined as the concentration below which no clinical response (either from safety signal like insomnia or from efficacy signal) is anticipated. The sponsor should provide the justification for the selected threshold. In addition, we agreed with the sponsor's proposal of using partial AUC to quantify early exposure. The sponsor should provide the justification on the selected time interval for partial AUC calculation.*

*We recommend that the sponsor assess between-subject variability using the two additional pharmacokinetic variables (time interval with no meaningful drug release and early exposure) with the data from the existing studies. We agreed that the planned dose proportionality studies could be modified to evaluate both between-subject variability and within-subject variability for all major pharmacokinetic parameters (including the two additional parameters). We recommend that sponsor submit the study protocol and data analysis plan for comments prior to initiating the trial.*

## **2.2. Clinical Pharmacology**

### **Justification for Not Conducting a Bioequivalence Study for HLD200**

**Question 3:** **Ironshore's clinical development plan is to evaluate the efficacy and safety of HLD200 in ADHD subjects in 2 phase 3 studies: 1) a laboratory classroom study (Study HLD200-107) and 2) an early-morning function study (Study HLD200-108). Draft protocols are provided in Appendix A in support of this development plan. In addition, there has been a recent change in manufacturing process for HLD200 (reference Section 5), and consequently, Ironshore has planned to conduct a clinical trial examining the PK effects of 100 mg of HLD200 in healthy adult volunteers in fasted, fed, and sprinkled states under a randomized, 3-way cross-over design with HLD200 (Study HLD200-109).**

***Does FDA agree that a bioequivalence study is not required with the conduct of the planned clinical studies highlighted above and that the studies will be adequate to evaluate HLD200?***

**Preliminary Comments:** *A bioequivalence study is not required if the sponsor is (a) not planning to bridge the PK data from any historical study and (b) all planned studies in*

*the future will use the new manufacturing process. However, a relative bioavailability study (against the Listed Drug Product) is required for the product made by the new manufacturing process.*

**Sponsor Response:**

- a. Ironshore changed the formulation from B-HLD200, C-HLD200 (54MG) (old formulation) to HLD200 (commercial formulation) during the development of the product. The old formulation, B-HLD200, was studied in a clinical study (HLD200-106) (b) (4). The commercial formulation will be studied in HLD200-107 and HLD200-108 which will (b) (4) demonstrate efficacy and safety of our product. The two formulations will provide independent efficacy and safety assessments, and hence, will not require further PK bridging of the formulations.
- b. We request further clarification regarding the Agency's comment about the requirement of the relative BA study against the Listed Drug Product. We have previously conducted a relative BA study using the old Ironshore formulation with Ritalin IR (HLD200-101). In our opinion: i) relative BA is typically not repeated for every formulation change across the clinical pharmacology studies, ii) we will be submitting the efficacy and safety assessment of the commercial formulation to support the registration of our product; and iii) we will be conducting dose-proportionality (HLD200-104) and food effect (HLD200-109) studies using the commercial formulation. We would like to understand from the Agency the scientific basis for repeating the relative BA study with the commercial formulation. Further, how will the results of the relative BA study inform drug development and/or regulatory decisions given the efficacy and safety assessments will be submitted?

**FDA Clarification on Sponsor's Response:** *We agree that a separate BA study comparing the commercial formulation (HLD200) to the Listed Drug is not necessary.*

*We noted your response under Question 5 stating that the differences between the two formulations are not major. Please include in the NDA a side-by-side comparison table with the specific details on the similarities and differences between the two formulations, manufacturing processes, etc., as well as the level of change (based on SUPAC-MR guidance). The acceptability of the bridging data based on in vitro dissolution testing alone will be determined during NDA review.*

**Discussion:** *No further discussion.*

**Justification for Not Conducting a Multiple-dose PK study for HLD200**

**Question 4:** Ironshore does not intend to conduct a multiple-dose PK study because 1) no accumulation is predicted with multiple dosing of HLD200 and 2) the predicted half-life and negligible accumulation with HLD200 are similar to that

observed with currently marketed formulations of MPH. A detailed justification for a request to waive a multiple-dose PK study is provided in Section 6.

*Does FDA agree that a multiple-dose PK study is not required and that the available pharmacokinetic information that will be obtained as part of the planned HLD200 studies (HLD200-104 and HLD200-109) as described Sections 8.1 and 8.2 in addition to information available for marketed formulations of MPH are adequate to describe the HLD200 PK?*

**Preliminary Comments:** *We conditionally agree that a formal multiple-dose PK study might not be required. However, the sponsors must demonstrate (using modeling and simulation) that there will be negligible accumulation on multiple-dosing based on the PK observed from the new formulation of HLD200.*

**Sponsor Response:** Agree.

**Discussion:** *No further discussion.*

### 2.3. 505(b)(2) NDA Submission Clinical Data Requirements

**Question 5:** Ironshore intends to submit a 505(b)(2) NDA inclusive of the following clinical studies:

- Phase 1 bioavailability study in adults using immediate-release (IR) Ritalin® as a comparator (completed)
- Phase 1/2 pharmacokinetic (PK) study in pediatric and adolescent ADHD patients (completed)
- Phase 1 fed-fasted-sprinkled food effect study in adults (completed)
- Phase 3 clinical endpoint evaluation study (CEES) in children 6 to 12 years of age (completed)
- Phase 1 dose proportionality study in adults after a single dose (planned)
- Phase 1 fed-fasted-sprinkled food effect study in adults (planned, manufacturing process change)
- Phase 3 efficacy and safety study in children 6 to 12 years of age evaluating post-waking, early morning function (b) (4) (planned)
- Phase 3 pivotal efficacy and safety study in children 6 to 12 years of age using the SKAMP scale (planned)

*Ironshore believes that the studies listed above, if conducted successfully, will generate sufficient clinical data to support approval of a 505(b)(2) NDA for HLD200 treatment of ADHD patients. Does the FDA agree?*

**Preliminary Comments:**

**Clinical Comments:**

- 1) *Please be advised that, given an apparent need for ADHD medication in many children under age 6 years, an approval of your application will carry a Postmarketing Requirement for a safety and efficacy trial in children ages 4 to 5 years. Because this requirement is new, and acceptable characteristics of such a trial have not yet been determined, this trial may be deferred. Your intention to conduct such a trial should be included in your initial Pediatric Study Plan (iPSP).*
- 2) *We note that you propose an indication for patients age 6 years and older. In general, because this claim would include the adult population, it must be supported by a separate safety and efficacy trial in adult patients. However, we are willing to consider an argument, which you may put forth in your application, that would convince us that a study in adults is unnecessary. If we are convinced, then a claim for the age range you propose (6 years and older) could be approved. If we are not convinced, the approved age range will be for patient ages 6 to 17, inclusive. Alternatively, you may elect to conduct a clinical trial in adults to support use in the adult age range.*

**Sponsor Response:** Agree

**Discussion:** *In view of the need for the parent of the patient to adjust the timing of evening dosing in accordance with early morning functioning, a potential requirement for a Human Factors Study was briefly discussed. It is not clear at this point that such a study will be required.*

**Clinical Pharmacology Comments:** *We have the following additional comments:*

- 1) *Relative bioavailability study: It needs to be repeated with the new manufacturing process for HLD200 vs. Listed Drug Product.*

**Sponsor Response:** Further clarification and discussion is requested in our EOP2 meeting.

**FDA Clarification on Sponsor's Response:** *Please see our clarification comments under Question 3.*

**Discussion:** *No further discussion.*

- 2) *Multiple ascending dose study: Perform simulation using the single-dose PK data (using new formulation) to predict no accumulation.*

**Sponsor Response:** Agree

**Discussion:** *No further discussion.*

- 3) *SAD study (HLD200-104): Please confirm that this SAD study is with the new formulation.*

**Sponsor Response:** Yes

**Discussion:** No further discussion.

- 4) *Alcohol effect study: Since a modified-release formulation is being developed, it is required to conduct in vitro alcohol dose-dumping studies to assess the impact of alcohol on the formulation and its drug-release characteristics. Based on the in vitro results, an in vivo (clinical) dose dumping study might or might not be recommended.*

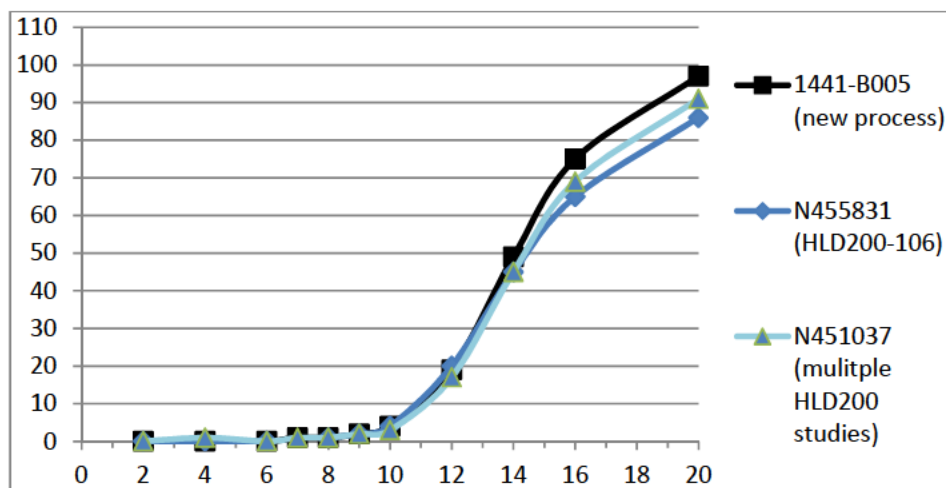
**Sponsor Response:** Agree

**Discussion:** No further discussion.

- 5) *SAD and relative BA study should be conducted prior to start of Phase 3 studies.*

**Sponsor Response:** We appreciate the Agency's view that conducting at least one PK study before the Phase 3 trials is prudent from a sponsor's risk point of view. However, we strongly believe that the PK profile of our product is well characterized in PK and Phase 3 trials. The commercial formulation will perform similarly based on our thorough understanding of the CMC changes. We would like to provide our justification for not performing the SAD prior to the Phase 3 studies.

- a. The changes to manufacturing process do not affect the release-controlling functional films of the modified-release product. The changes are limited to a change from (b) (4)
- b. A comparison of in-vitro dissolution performance for the new manufacturing process (lot 1441-B005) to the old manufacturing process (clinical lots N455831 and N450137) shows an approximate 6-10% difference in drug release at the 20 hour time point and no important difference prior to the 14 hour time point of dissolution. The 6% increase in dissolution only increases the predicted  $AUC_{0-\infty}$  by 6%, from 169.2 to 179.4 ng·hr/ml, which is not clinically significant.



- c. There is no a priori reason to believe the in vivo PK profile will be meaningfully different between the old and the commercial formulations.

For the reasons outlined above, Ironshore believes that the risk of a clinically significant difference between product manufactured with new and old manufacturing processes is minimal and thus we do not intend to complete the SAD study prior to initiation of the HLD200-107 or HLD200-108 studies. Does the Agency agree?

**FDA Clarification on Sponsor's Response:** *We accept the sponsor's rationale.*

**Discussion:** *No further discussion.*

*Please confirm that all planned studies from this point onwards will be conducted using the new formulation.*

**Sponsor Response:** Yes.

**Discussion:** *No further discussion.*

**Additional Biometrics Comments:**

*The purpose of this meeting is to discuss the clinical development program. Because of very limited review time for the briefing document, we can only focus on certain key elements included in your draft protocols. In order for us to review the protocols or SAPs in detail, please submit them in a serial separate from a meeting package.*

**Sponsor Response:** Agree.

**Discussion:** *No further discussion.*

### 3.0 **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

#### **4.0 DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

#### **5.0 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

[CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm)  
(<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm> ).

## **6.0     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.

| <b>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</b> |                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Source of information<br/>(e.g., published literature, name of<br/>listed drug)</b>                                                                                                                                | <b>Information Provided<br/>(e.g., specific sections of the 505(b)(2)<br/>application or labeling)</b> |
| <i>1. Example: Published literature</i>                                                                                                                                                                               | <i>Nonclinical toxicology</i>                                                                          |
| <i>2. Example: NDA XXXXXX<br/>“TRADENAME”</i>                                                                                                                                                                         | <i>Previous finding of effectiveness for<br/>indication X</i>                                          |
| <i>3. Example: NDA YYYYYY<br/>“TRADENAME”</i>                                                                                                                                                                         | <i>Previous finding of safety for<br/>Carcinogenicity, labeling section XXX</i>                        |
| <i>4.</i>                                                                                                                                                                                                             |                                                                                                        |

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.

## **7.0 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).

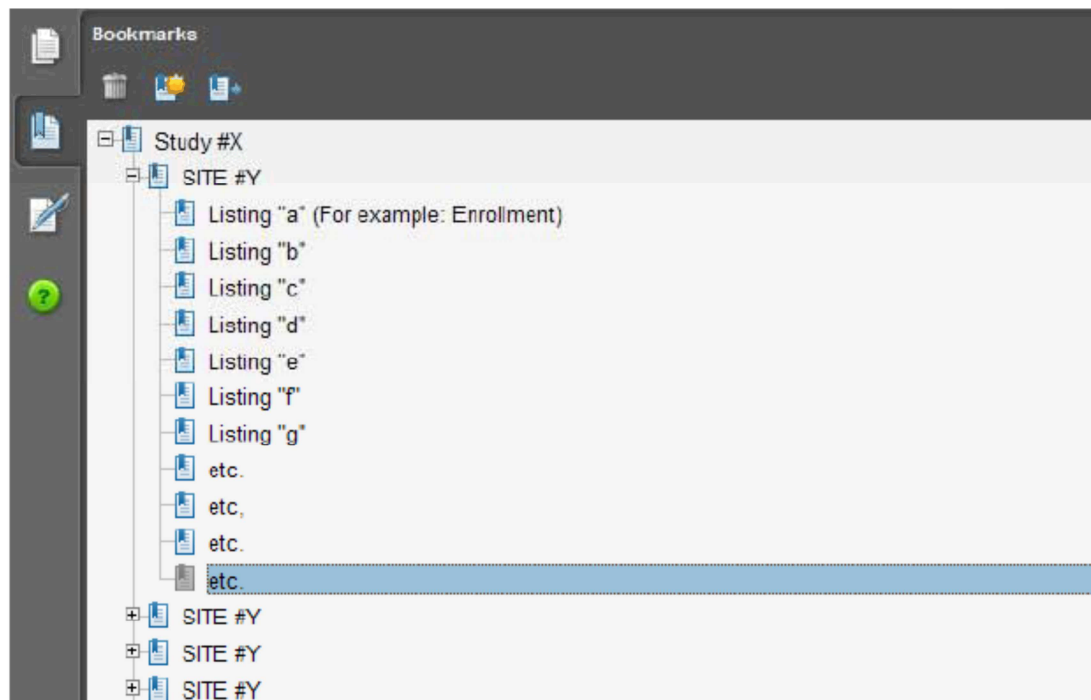
**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

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.”

| <b>DSI Pre-NDA Request Item<sup>4</sup></b> | <b>STF File Tag</b>          | <b>Used For</b>                                     | <b>Allowable File Formats</b> |
|---------------------------------------------|------------------------------|-----------------------------------------------------|-------------------------------|
| 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<br>(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.

<sup>4</sup> 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](mailto:ESUB@fda.hhs.gov)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MITCHELL V Mathis  
04/15/2015