CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215430Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 124813

MEETING MINUTES

Axsome Therapeutics, Inc.
Attention: Melina Cioffi, PharmD
Executive Director, Regulatory Affairs
200 Broadway, 3rd Floor
New York, NY 10038

Dear Dr. Cioffi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AXS-05 (Dextromethorphan HBr/Bupropion HCl).

We also refer to the telecon between representatives of your firm and the FDA on June 11, 2020. The purpose of the meeting was to discuss the content and format of an NDA submission.

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

If you have any questions, please contact CAPT Bill Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, M.D.
Director (Acting)
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 11, 2020 from 12:00 pm to 1:00 pm
Meeting Location: Webex Only

Application Number: IND 124813
Product Name: AXS-05 (Dextromethorphan HBr/Bupropion HCl)
Indication: Major Depressive Disorder (MDD)
Sponsor Name: Axsome Therapeutics, Inc.
Regulatory Pathway: 505(b)(2) of the Food, Drug, and Cosmetics Act

FDA ATTENDEES

Billy Dunn, MD	Director (Acting), Office of Neuroscience (ON)
Eric Bastings, MD	Deputy Director (Acting), ON
Tiffany R. Farchione, MD	Director (Acting), Division of Psychiatry (DP)
Bernard Fischer, MD	Deputy Director (Acting), DP
Michael Davis, MD, PhD	Clinical Team Leader, DP
David Millis, MD	Clinical Reviewer, DP
Ikram Elayan, PhD	Supervisor, Division of Pharmacology/ Toxicology for Neuroscience (DPT-N)
Arippa (Ravi) Ravindran, PhD	Pharmacology/Toxicology Reviewer, DPT-N
Luning (Ada) Zhuang, PhD	Team Leader, Office of Clinical Pharmacology (OCP)
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, OCP
Julia Pinto, PhD	Product Quality Branch Chief, Office of Pharmaceutical Quality (OPQ)
Valerie Amspacher, PharmD	Product Quality Team Leader, OPQ
Andrei Ponta, PhD	Product Quality Reviewer, OPQ
Ta-Chen Wu, PhD	Biopharmaceutics Team Leader, OPQ
Peiling Yang, PhD	Statistics Team Leader, Office of Biostatistics (OB)
Semhar Ogbagaber, PhD	Statistics Reviewer, OB
Katherine Bonson, PhD	Controlled Substance Staff (CSS) Reviewer
Colleen LoCicero, RPh	Regulatory Policy Advisor, ON
Bill Bender, RPh	Senior Regulatory Project Manager, Division of Regulatory Operations for Neuroscience (DRON)—Psychiatry Group

SPONSOR ATTENDEES

Herriot Tabuteau, MD	Chief Executive Officer
Mark Jacobson, MA	Chief Operations Officer
Amanda Jones, PharmD	Senior VP, Clinical Research

Cedric O'Gorman, MD, MBA	Senior VP, Clinical Development & Medical Affairs
Melina Cioffi, PharmD	Executive Director, Regulatory Affairs
Daniel Bigelow	Manager, Regulatory Affairs
Michael Chen, PhD	Statistician
John Dillberger, PhD	Non-clinical

1.0 BACKGROUND

Axsome is developing AXS-05 for the treatment of major depressive disorder (MDD) [redacted] (b) (4) AXS-05 is an oral, fixed-dose combination of bupropion HCl 105 mg and dextromethorphan HBr (DM) 45 mg. Bupropion, an inhibitor of norepinephrine and dopamine reuptake, is approved for the treatment of depression. DM is an N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, and inhibitor of the serotonin transporter (SERT) and norepinephrine transporter (NET). DM is quickly eliminated because of extensive metabolism through CYP2D6. The bupropion component of AXS-05 competitively inhibits the metabolism of DM and thus increases its plasma concentration. The Sponsor is pursuing an NDA through the 505(b)(2) pathway referencing the listed drugs Wellbutrin SR (bupropion) and Nuedexta (a fixed-dose combination of dextromethorphan HBr and quinidine sulfate approved for the treatment of pseudobulbar affect).

The Sponsor proposes to submit data from the following completed trials in support of the NDA:

1. *Study AXS-05-MDD-201 (ASCEND): Treatment of MDD*

   This was a phase 2 randomized, double-blind, active-controlled, multi-center U.S. trial in which 80 adults diagnosed with moderate to severe MDD were randomized to treatment with either AXS-05 or bupropion 105 mg twice daily for 6 weeks. The primary efficacy endpoint was the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score, calculated at each time point in the study and averaged. The primary efficacy endpoint was met; the mean change from baseline in MADRS total score was 13.7 points for AXS-05, compared to 8.8 points for bupropion ($p < 0.001$).

2. *Study AXS-05-MDD-301 (GEMINI): Treatment of MDD*

   This was a phase 3 randomized, double-blind, placebo-controlled, multi-center U.S. trial in which 327 adults diagnosed with moderate to severe MDD were randomized to treatment with either AXS-05 or placebo once daily for 3 days and twice daily thereafter for a total of 6 weeks. The primary efficacy endpoint was change from baseline in the MADRS total score at Week 6. The primary efficacy endpoint was met. The change from baseline in MADRS total score was 16.6 points for AXS-05 compared to 11.9 points for placebo ($p = 0.002$).

3. *Study AXS-05-301 (STRIDE): Treatment of TRD*

   This was a phase 2/3 randomized, double-blind, active controlled trial. During a 6-week lead-in period, 799 patients with MDD who had previously failed one or two antidepressants were treated in an open-label fashion with 150 mg bupropion twice daily. The 312 patients who failed to respond to bupropion were randomized to treatment with either bupropion 150 mg or AXS-05 twice daily for 6 weeks. The primary efficacy endpoint was the change from baseline in the MADRS total score at Week 6. The primary efficacy endpoint was not met. The change from baseline in MADRS total score was 11.6 points for AXS-05 compared to 9.4 points for bupropion ($p = 0.117$). (b) (4) (b) (4)

4. *Study AXS-05-303: Long-Term Safety Study*

   The Sponsor has initiated an open-label, multi-center, U.S. long-term safety study. The study anticipates enrolling enough patients to ensure at least 300 patients are treated for at least 6 months and 100 patients for at least 12 months. The expected time frame for completion is November 2020.

The safety database to support the NDA will consist of over 1500 patients exposed to at least one dose of AXS-05, at least 300 patients exposed for at least 6 months, and at least 100 patients exposed for at least 12 months. The safety database will include patients participating in trials for treatment of MDD, TRD, and agitation associated with Alzheimer's disease (IND (b) (4)), as well as healthy volunteers.

The Sponsor's stated purpose for this meeting is to reach agreement on the content and format of the planned NDA submission for the approval of AXS-05 for the treatment of MDD. The Sponsor intends to reach consensus with FDA on the following:

1. The overall content and format of the planned 505(b)(2) NDA;
2. The efficacy and safety evaluations to be presented in the planned NDA;
3. The scope of safety data and timing of submission of these data;
4. Clinical pharmacology studies required to support NDA submission;
5. Nonclinical studies to be presented in the planned NDA.

2.0 DISCUSSION

2.1. Clinical

Question 1: Axsome is planning an NDA submission for the use of AXS-05 in the treatment of MDD, in accordance with the agreement reached at the Breakthrough Therapy Designation meeting held on April 3, 2019 between Axsome and FDA, where it

was agreed that positive results of Studies AXS-05-MDD-201 (ASCEND) and AXS-05-MDD-301 (GEMINI) would support an indication for AXS-05 in the treatment of MDD.

In light of the positive results from these studies that are now available, does the Division agree with the Sponsor's plan to submit an NDA using these data to support a clinical review of AXS-05 for the treatment of MDD?

See Section 5.2 for supporting justification.

FDA Response to Question 1: *Yes, we agree with this plan. We note that Study AXS-05-MDD-201 was originally submitted as a phase 2 study designed to evaluate the safety and tolerability of AXS-05 and bupropion in subjects with MDD. The primary efficacy endpoint (mean change from baseline in MADRS total score, averaged across all visits), which did not appear in the study protocol but was added to the Statistical Analysis Plan later, has not previously been used to support regulatory approval of an antidepressant. More typically, we would use the mean change from baseline to end of treatment in MADRS total score (without averaging across visits). The primary analysis, LOCF ANCOVA, is also difficult to justify unless the dropout rate is negligible. In your NDA submission, you should include justifications for the suitability of the primary analysis as well as sensitivity analyses to assess the impact of the improbable missing data assumptions under the primary analysis. The acceptability of Study AXS-05-MDD-201 to support approval of your product will be a matter of review.*

Discussion: *No further discussion.*

Question 2: Does the Division consider the Sponsor's anticipated NDA safety database to be acceptable?

See Section 8.3 for supporting justification.

FDA Response to Question 2: *Yes, the anticipated safety database will fulfill the ICH E1 Guideline once the open-label safety study is complete.*

Discussion: *No further discussion.*

Question 3: Does the Division concur with the Sponsor's plan to provide patient narratives?

See Section 8.2.2 for supporting justification.

FDA Response to Question 3: *Yes, we agree with the plan to provide patient narratives and corresponding CRFs for deaths, serious adverse events (SAEs), and discontinuations due to an adverse event.*

Discussion: *No further discussion.*

Question 4: Does the Division concur with the Sponsor's planned content for the 120-day safety update?

See Section 8.3.1 for supporting justification.

FDA Response to Question 4: *Yes, we agree with the plan to include a final CSR and data set for the open-label study in the NDA submission. If the final CSR for the open-label study is not yet available at the time of the NDA filing, an interim CSR may be included in the NDA submission. We agree with the plan to include SAEs from any ongoing studies in the initial NDA, with a cut-off date 3 months prior to submission, and to include updated safety information in the 120-Day Update.*

Discussion: *No further discussion.*

Question 5: Does the Division agree with the Sponsor's proposal to utilize the text portion of the integrated summaries of safety and efficacy (Module 5.3.3) as the Clinical Summaries of Efficacy (Module 2.7.3) and Safety (Module 2.7.4)?

See Section 8.5 for supporting justification.

FDA Response to Question 5: *Yes, we agree with this plan.*

Discussion: *No further discussion.*

Question 6: The Division agreed that the change in MADRS at Week 1 and at Week 2 were acceptable key secondary endpoints that could be described in labeling in replicated (email from FDA dated January 23, 2020). Does the Division agree that the replicated early efficacy data, change in MADRS at Weeks 1 and 2 from Study AXS-05-MDD-301 (GEMINI), at Week 2 from Study AXS-05-MDD-201 (ASCEND), and at Weeks 1 and 2 from Study AXS-05-301 (STRIDE-1), are sufficient to support a description of these key secondary endpoints in product labeling?

See Sections 5.2.1.2.2, 5.2.2.2.3, and 5.3 for supporting justification.

FDA Response to Question 6: *The details of product labeling will be a matter of our final review of data from each of the three studies.*

Discussion: *No further discussion.*

2.2. Statistics

Question 7: Does the Division agree with the Sponsor's planned integrated presentation of efficacy and safety?

See Section 8.1 and 8.2 for supporting justification.

FDA Response to Question 7: *Yes, we agree with this plan for the Integrated Summary of Efficacy and the Integrated Summary of Safety. However, pooled analyses can only be considered exploratory.*

Additional Comments from Statistics
For the randomized trials identified as supporting efficacy, please include in your NDA submission the following:

a. *All raw as well as derived variables in .xpt format*

b. *The SAS programs that produced all efficacy (primary and key secondary endpoints) results*

c. *The SAS programs by which the derived variables were produced from the raw variables*

d. *A listing of corresponding history pertaining to this IND/NDA including serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*

Discussion: *No further discussion.*

2.3. Clinical Pharmacology

Question 8: Does the Division agree with the Sponsor's plan for evaluating the pharmacokinetics of AXS-05 in CYP2D6 poor metabolizers?

See Section 6.2.2.3 for supporting justification.

FDA Response to Question 8: *No, we do not agree. You must have a group of CYP2D6 extensive metabolizers in the study as a control to evaluate the effect of CYP2D6 poor metabolizer status on PK after administration of your product. A cross-study comparison is not recommended.*

Discussion: *The Sponsor agreed to include both CYP2D6 extensive metabolizers and CYP2D6 poor metabolizers in the proposed study.*

Question 9: Does the Division agree with the Sponsor's plan to bridge the drug-drug interactions of AXS-05 to the reference listed drugs, Wellbutrin® and Nuedexta®?

See Section 6.2.4 and Appendix 2: Proposed Drug Interaction Section for Labeling for AXS-05 for supporting justification.

FDA Response to Question 9: *You may rely on FDA's findings of safety and/or effectiveness for a listed drug or drugs—including FDA's findings with respect to drug interactions—to support a 505(b)(2) NDA provided that you meet all the requirements for reliance on a listed drug (including establishing an acceptable bridge to justify the reliance). We note that it may be also acceptable to rely on information pertinent to DM from other sources, such as information in published literature. You will need to provide the data necessary to inform the safe and effective use of your proposed product pertaining to drug interactions if you are not able to rely on published literature or Agency findings (i.e., with respect to a listed drug or drugs). Ultimately, labeling will be discussed after the NDA is filed.*

Additional Comments from Clinical Pharmacology

a. *If you intend to submit a 505(b)(2) application that relies on FDA's findings for one or more listed drugs, you will need to establish an appropriate scientific bridge to each listed drug on which you intend to rely. Please clarify how you have or intend to establish an appropriate scientific bridge to each listed drug on which you intend to rely for approval.*

b. *PK information on the interaction potential between DM and bupropion (i.e., DM on bupropion, and bupropion on DM) needs to be submitted in the NDA package.*

c. *To provide specific dosing instructions, you will need to evaluate the effect of CYP2B6 inducers/inhibitors on the exposure of DM after administration of your product. Because strong/moderate CYP2B6 inhibitors are not currently identified, we recommend you conduct a study with clopidogrel or prasugrel. Clopidogrel or prasugrel are known to inhibit CYP2B6 activities, and likely to be commonly administered concurrently with antidepressants in the clinic. For strong inducers of CYP2B6, carbamazepine is recommended on the Agency's Drug Development and Drug Interactions website.*

d. *We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry,* Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*. Consider strategies to enhance clarity, readability, and comprehension of*

this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Discussion: *See Sponsor's attached slides. The Sponsor agreed: a) to submit PK information for both DM and BUP on the interaction potential between the two moieties in the NDA package; b) to conduct two additional DDI studies with clopidogrel and carbamazepine, respectively. After confirmation from the Sponsor that "In vitro cytochrome P450 inhibition/induction data for DM" is the only piece of information they plan to rely on from Nuedexta for their 505(b)(2) application, the Division recommended, and Sponsor agreed to, generation of their own in vitro data regarding CYP induction/inhibition potential at relevant DM concentration levels. Therefore, reliance on Nuedexta for this 505(b)(2) application does not seem necessary from a clinical pharmacology perspective.*

2.4. Nonclinical

Question 10: The 3-month bridging general toxicity and embryo-fetal developmental (EFD) toxicity studies, requested by the FDA in the Pre-IND meeting minutes as the only additional non- clinical studies needed to submit an NDA for AXS-05 via the 505(b)(2) route, have been conducted by the Sponsor. Also as agreed in the Pre-IND meeting minutes, the Sponsor will include the existing nonclinical data on bupropion, DM, and the combination of DM and quinidine, in the current product inserts for Wellbutrin® and Wellbutrin SR® (bupropion), and Nuedexta® (dextromethorphan/ quinidine) in the NDA application. Does the Division agree that this nonclinical package is adequate to support the filing of an application of AXS-05 for the treatment of MDD?

See Section 7 for supporting justification.

FDA Response to Question 10: *On face, the nonclinical package appears to be sufficient to support the filing of an NDA application; however, adequacy of the bridging studies will be a matter of review.*

Discussion: *The non-clinical team requested that the Sponsor provide a justification as to why the mouse is the most relevant species and how the data from the mouse studies will provide a bridge to the non-clinical data in the different sections of the label of the listed drug. The Sponsor agreed to submit the justification to the IND for our review before filing the NDA.*

2.5. Procedural

Question 11: Based on the Breakthrough Therapy Designation of AXS-05, Axsome intends to request a priority review of the NDA for AXS-05 for the treatment of MDD. Does the FDA intend to grant this request?

See Section 8.7 for supporting justification.

FDA Response to Question 11: *Please refer to Appendix 1 (C) in the FDA Guidance for Industry on Expedited Programs for Serious Conditions on the procedures for submitting a priority review designation request. The Agency will review the justification submitted with your NDA and inform you of our priority review decision by day 60 of the review.*

Discussion: *No further discussion.*

Question 12: Does the Division agree that the Sponsor's content and format to be adequate to support the filing of an application of AXS-05 for the treatment of MDD?

See Appendix 1: NDA Table of Contents for AXS-05 in the Treatment of MDD for supporting justification.

FDA Response to Question 12: *Yes, we agree. Please follow the additional guidance in the section "Data Standards for Studies" below.*

Discussion: *No further discussion.*

2.6. Abuse Potential

Question 13: Does the Division agree with the Sponsor's plan for assessing the abuse potential of AXS- 05 in the NDA submission?

See Section 8.6 for supporting justification.

FDA Response to Question 13: *Yes, we agree that a comprehensive evaluation of abuse-related adverse events produced by AXS-05 in all clinical studies in comparison to its components and placebo, will provide an adequate assessment of the abuse potential of AXS-05. The presentation of the abuse-related AEs in the Abuse Potential Assessment of the NDA should follow the recommendations in the 2017 Guidance for Industry: Assessment of the Abuse Potential of Drugs.*

Discussion: *No further discussion.*

Additional Agency Comment
The Agency Biopharmaceutics team is completing their review of your briefing package. They may have additional comments or questions during the meeting or as a separate communication.

Discussion: *The Sponsor plans to submit a separate CMC meeting; therefore, the Biopharmaceutics team will defer comments/discussion to that meeting.*

3.0 OTHER

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[3]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[4]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[5]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide, [6] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards.

[3] http://www.fda.gov/ectd
[4] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[5] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[6] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[7] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[8] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[9] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the

[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[9] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[10] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[11]

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[12]

MANUFACTURING FACILITIES

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

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

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

[10] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[12] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[13] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[14]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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).[15] 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 Regulations.gov.[16]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such

[13] https://www.fda.gov/media/84223/download
[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[15] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[16] http://www.regulations.gov

reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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

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

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

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

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on

published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

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

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[17]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's slides in response to Agency preliminary comments are attached.

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[17] https://www.fda.gov/media/85061/download

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

/s/

TIFFANY R FARCHIONE
07/07/2020 11:08:48 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124813

MEETING MINUTES

Axsome Therapeutics, Inc.
Attention: Cedric O'Gorman, MD, MBA
Senior Vice President, Clinical Development
25 Broadway, 9th Floor
New York, NY, 10004

Dear Dr. O'Gorman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for XS-05 (Bupropion HCL/Dextromethorphan HBr).

We also refer to the meeting between representatives of your firm and the FDA on April 3, 2019. The purpose of the meeting was to discuss the requirements of your planned NDA filing.

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, please contact CAPT Bill Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, M.D.
Director (Acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2 (EOP2)

Meeting Date and Time: April 3, 2019 from 1:00 pm to 2:00 pm
Meeting Location: WO, Bldg 22, Room 1315

Application Number: IND 124813
Product Name: AXS-05 (Bupropion HCL/Dextromethorphan HBr)
Indication: Major Depressive Disorder (MDD) (b) (4) (b) (4)

Sponsor/Applicant Name: Axsome Therapeutics, Inc.

FDA ATTENDEES

Tiffany R. Farchione, MD	Director (Acting), DPP
Michael Davis, MD	Clinical Team Leader, DPP
David Millis, MD	Clinical Team Reviewer, DPP
Ikram Elayan, PhD	Pharmacology/Toxicology Supervisor, DPP
Ravi Ravindran, PhD	Pharmacology/Toxicology Reviewer, DPP
Ada Zhuang, PhD	Clinical Pharmacology Team Leader, OCP
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Statistics Team Leader, Division of Biometrics I (DBI)
Semhar Ogbagaber, PhD	Statistics Reviewer, DBI
David Claffey, PhD	Product Quality Team Leader, OMPT
Andrei Ponta	Product Quality Reviewer, OMPT
Jovita Randall-Thompson. PhD	Pharmacologist Reviewer, CSS
Ellis Unger, MD	Office Director, ODE1
Bill Bender, RPh	Senior Regulatory Project Manager

SPONSOR ATTENDEES

Herriot Tabuteau, M.D.	Chief Executive Officer
Cedric O'Gorman, M.D., M.B.A.	Senior VP, Clinical Development & Medical Affairs
Mark Jacobson, M.A.	Senior VP, Operations
Amanda Jones, Pharm.D.	Executive Director, Clinical
Research Karen TenHuisen	Senior Director, CMC
Daniel Bigelow	Senior Associate, Research and Operations
Michael Chen, Ph.D.	Statistician
John E. Dillberger, D.V.M, Ph.D.	Nonclinical Pharmacology

1.0 BACKGROUND

Axsome is developing AXS-05 (bupropion and dextromethorphan) for the treatment of major depressive disorder (MDD) (b) (4) AXS-05 is an oral, fixed-dose combination of dextromethorphan (DM) and bupropion. The DM component of AXS-05 is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, a sigma-1 receptor agonist, an inhibitor of the serotonin and norepinephrine transporters, and a nicotinic acetylcholine receptor antagonist. DM is quickly eliminated due to extensive metabolism through CYP2D6, yielding low systemic exposure when given as a single agent even at high and repeated doses. The bupropion component of AXS-05 serves to increase the plasma concentrations of DM into a potentially therapeutic range by inhibiting its metabolism. In addition, bupropion is a norepinephrine and dopamine reuptake inhibitor that is approved as a treatment for MDD.

The pharmacokinetics of the components of AXS-05 (bupropion and DM) in specific populations have been reported in the FDA package inserts for several approved bupropion- and DM-containing products. Results of clinical drug interaction studies, in which target drugs were co-administered with the individual components of AXS-05 (bupropion or DM) or with the combination of DM and quinidine, have also been reported in the FDA package inserts for approved bupropion- and DM-containing products. Axsome intends to reference the pharmacokinetic information in specific populations, and the clinical drug interaction information, in these package inserts in support of their planned 505(b)(2) NDA filing for AXS-05.

The clinical development program for AXS-05 to date is comprised of a recently completed positive phase 2 trial in MDD (Study AXS-05-MDD-201) and an ongoing phase 2/3 trial in TRD (Study AXS-05-301). The primary efficacy endpoint for the Study AXS-05-MDD-201 was mean change from baseline in the total score on the Montgomery Asberg Depression Rating Scale (MADRS). Eighty subjects were randomized in a 1:1 ratio to receive six weeks of treatment with either bupropion 105 mg bid or AXS-05 45 mg dextromethorphan / 105 mg bupropion bid. The results showed greater improvement in depressive symptoms for patients treated with AXS-05 than for patients treated with bupropion. The results from this study supported the granting of Breakthrough Therapy Designation for the treatment of MDD on March 25, 2019. Axsome intends to initiate a phase 3 trial in MDD which, in conjunction with the currently ongoing phase 2/3 TRD trial and the completed phase 2 MDD trial, would support an NDA filing of AXS-05 for the treatment of MDD (b) (4)

The purpose of this meeting is to discuss the planned NDA filing for AXS-05 for the (b) (4) (b) (4) and the planned phase 3 trial in MDD. The Sponsor would like to reach consensus on the following:

1. The clinical trials required to support an NDA filing under 505(b)(2) for treatment of MDD (b) (4);
2. The proposed phase 3 trial in MDD, including selection of inclusion/exclusion criteria;
3. CMC information to support an NDA filing;

4. Clinical pharmacology studies to support an NDA filing; and
5. Nonclinical bridging toxicology studies to support an NDA filing.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls Questions

Question 1: Axsome intends to update the drug product testing to include a specification for (b) (4) content and update identification testing so it is specific to the new drug substance (e.g. via FT-IR) to address the Division's request in the Study May Proceed letter dated February 23, 2016. Does the Division agree that no further updates to drug product testing are required to support an NDA?

FDA Response to Question 1: *The adequacy of the release and stability drug product specifications will be a matter for review; however, the proposed specifications appear reasonable.*

Discussion: *No further discussion.*

Question 2: Upon completion of all development and optimization work, Axsome plans to produce three registration batches at a scale of (b) (4) tablets per batch to support an NDA. Does the Division agree this is an appropriate batch size to support an NDA filing?

FDA Response to Question 2: *There is not enough information in the meeting package to address this question as the commercial batch size is not provided. We recommend adhering to the ICH Q1A (R2) guideline, "Stability Testing of New Drug Substances and Products." Per the guidline, two of the three primary batches should be at least pilot scale batches and the third one can be smaller, if justified.*

Discussion: *No further discussion.*

Question 3: Axsome expects to have at least 24 months of stability data from currently ongoing stability studies and at least 6 months of stability data on the planned registration batch material at the time of NDA filing. Does the FDA agree these data would be sufficient to support an NDA filing?

FDA Response to Question 3: *We expect the initial NDA to contain 6-month accelerated and at least 12-month long-term stability data for three representative drug product batches manufactured using the proposed commercial manufacturing process and packaged in the proposed commercial container closure system. For detailed recommendations regarding the batch selection, testing conditions, etc., refer to ICH Q1A (R2).*

Discussion: *No further discussion.*

2.2. Nonclinical Questions

Question 4: To support an NDA filing, Axsome is currently completing a 3-month repeat-dose toxicity study of AXS-05 in mice, and intends to initiate an embryofetal developmental (EFD) toxicity study of AXS-05 in mice. Pending review of the data from these studies, does the FDA agree that these bridging toxicity studies will be an adequate package of nonclinical studies to support an NDA filing?

FDA Response to Question 4: *Based on the information provided in the background package, it is not clear why mouse and not rabbit will be used for the Segment II bridging study (referencing your letter dated 2/16/2016 regarding our phone conversation on this matter). However, based on an acceptable rationale the adequacy of the studies including the 3-month mouse toxicity study will remain a matter of review when the full nonclinical package is submitted. We also want to remind you that as per our initial communication at/following the pre-IND meeting with the Division (2/26/2015 Meeting Minutes), both studies will be needed at an appropriate time to support your phase 3 clinical trial. You have indicated that the toxicity study has been conducted and will be submitted soon; however, the Seg II animal study has not been started. This study could be conducted in parallel with the phase 3 clinical study; however, women of child bearing potential should be protected by using two forms of contraception if included in these studies.*

> ***Discussion:*** *The Division inquired about the rationale for using the mouse and not the rabbit in the Segment II bridging study and the Sponsor indicated that the mouse appears to be a better model than the rat given that it is closer to the human PK profile. The Sponsor added that the mouse is another species that could also be used for these studies. The Division did not object to the rationale and indicated that the validity of the studies will be a review issue. Post meeting, the Sponsor's preclinical consultant indicated to the non-clinical supervisor, Dr. Elayan, that he was not clear on the previous discussion between the Division and the Sponsor about using the rabbit (referenced in the FDA response above) and that the mouse would still be an appropriate species to be used for these studies. The non-clinical supervisor reiterated that the mouse could be a valid choice; however, the validity of the studies will be a review matter.*

2.3. Clinical Questions

Question 5: Can the ongoing Phase 2/3 trial in TRD (Study AXS-05-301), if successful, along with the completed Phase 2 trial in MDD (Study AXS-05-MDD-201), serve to adequately support an NDA filing for the indication of treatment of MDD?

FDA Response to Question 5: *We agree that Study AXS-05-301 in TRD, if positive, and Study AXS-05-MDD-201 could support an NDA filing for the indication of treatment of MDD, considering that patients with TRD also have the diagnosis of MDD.* (b) (4) (b) (4) *(please see response to Question 6d).*

Discussion: *No further discussion.*

Question 6: Axsome is proposing a Phase 3, randomized, double-blind, placebo-controlled, trial of AXS-05 in patients with MDD. Subjects who meet the DSM-5 criteria for MDD without psychotic features, and with a MADRS score of ≥ 25, will be randomly assigned to treatment with AXS-05 (105 mg bupropion and 45 mg dextromethorphan) or placebo, twice daily for 6 weeks. The primary endpoint will be the change from baseline in the MADRS total score at Week 6.

In this trial, the diagnosis of MDD with a current major depressive episode of moderate or greater severity will be confirmed by an independent assessor based on clinical review and a QIDS-SR-16 score of ≥ 13 at Screening or Baseline. Only subjects whose diagnosis is confirmed by the independent assessor will be analyzed for efficacy. Investigators and study subjects will be blinded to the confirmation of diagnosis. In order to maintain the blinding of study investigators and to further minimize bias, subjects without a confirmed diagnosis, as determined by the independent assessor, will be randomized and analyzed for safety.

a. Is the proposed study design acceptable to the FDA?

FDA Response to Question 6a: *We are unclear on the plan for using the diagnostic assessment of the independent assessor in the screening process. Typically, if the independent assessor does not agree that the patient meets the diagnostic criteria for study inclusion, this would be considered a screen failure. If such patients enter the study, the analysis of study results is complicated by the inclusion of screen failures in the randomization population. In addition, this introduces the safety risks of drug exposure to patients who did not meet all of the study inclusion criteria and therefore may not be expected to benefit from drug exposure. Please clarify the role of the independent diagnostic assessment in the study design if it is not being used to identify patients who should not be randomized.*

Discussion: *The Sponsor clarified that the purpose of the independent assessment is to ensure that enrolled patients meet the study criteria, and that only patients whose diagnosis is confirmed by the independent assessor will be randomized. The independent assessment will consist of a review of a subject's clinical records and the results of assessment measures from screening. An example of an issue that the independent assessor will consider is inconsistency between the patient self-report of depressive symptoms on the Quick Inventory of Depressive Symptomatology (QIDS) and the clinician rating on the MADRS. Alignment between the patient-reported and clinician-reported measures of depression symptoms would be reassuring to the independent assessor and support randomization..*

b. Is the use of the MADRS for assessing efficacy acceptable to the FDA?

FDA Response to Question 6b: *The Agency agrees to the use of the MADRS-10 as an efficacy endpoint in clinical trials of antidepressants. We want to clarify that we do not accept the MADRS-6 as an appropriate efficacy endpoint for antidepressant clinical trials. The full MADRS-10 should be used.*

Discussion: *No further discussion.*

c. As agreed in the Pre-IND meeting minutes dated 11 March 2015 (Question 9), the ongoing Phase 2/3 trial in TRD (Study AXS-05-301), which utilizes a bupropion comparator, if successful, will satisfy the fixed combination drug product requirements (21 CFR 300.50). In addition, Axsome believes that the completed Phase 2 trial (Study AXS-05-MDD-201), which was conducted with a bupropion comparator, also satisfies the fixed combination drug product requirements. Therefore it is appropriate for this proposed Phase 3 trial in MDD to utilize only a placebo control. Does the FDA agree?

FDA Response to Question 6c: *We agree that the completed phase 2 trial, Study AXS-05-MDD-201, and the ongoing phase 2/3 trial, Study AXS-05-301, if successful, will satisfy the fixed combination drug product requirements. We understand that dextromethorphan, if given alone at the dosage used in AXS-05, would be metabolized too quickly to allow the direct evaluation of its effects on symptoms of depression. To date, Study AXS-05-MDD-201 appears to have demonstrated that dextromethorphan contributes an antidepressant effect beyond the antidepressant effect of bupropion. Thus, we agree that the proposed phase 3 trial may be designed to include only a placebo control.*

Discussion: *No further discussion.*

d. Can this proposed Phase 3 trial in MDD and the ongoing Phase 2/3 trial in TRD (Study AXS-05-301), if they are successful, along with the completed Phase 2 trial in MDD (Study AXS-05-MDD-201), serve to adequately support an NDA filing (b) (4) (b) (4)

FDA Response to Question 6d: *The combination of a phase 2 trial in MDD, a Phase 3 trial in MDD, and a phase 2/3 trial in TRD would support an NDA filing for the indication of treatment of MDD.* (b) (4)

Please be aware that whether the completed Study AXS-05-MDD-201 is considered positive will be a matter of review. The primary efficacy analysis is based on LOCF MMRM. Unless the dropout rates are negligible, inferences based on the LOCF imputation approach are more likely to be biased as they would likely overestimate or underestimate treatment effects.

Discussion: *The Agency clarified that the completed phase 2 trial in MDD and the proposed phase 3 trial in MDD could support the MDD indication.* (b) (4)

[redacted] (b) (4)

Question 7: Axsome intends to initiate an open-label safety extension trial in which subjects who have participated in a prior MDD or TRD study with AXS-05 will be treated with AXS-05 and followed for up to 1 year. Is this acceptable?

FDA Response to Question 7: *This is acceptable.*

Discussion: *No further discussion.*

Question 8: It is our intention to submit an NDA for AXS-05, using the 505(b)(2) pathway, with a safety database of approximately 400 subjects, with approximately 100 treated for 6 months and approximately 50 treated for 1 year. Axsome believes that this safety database is sufficient for the filing on our planned NDA. Does the FDA agree?

FDA Response to Question 8: *Per the ICH E1 Guideline, the safety database should include at least 1500 subjects with short-term exposure to the investigational drug, 300 to 600 subjects with exposure for at least six months, and 100 subjects with exposure for at least a year. Although the combination of dextromethorphan and quinidine is approved for chronic use, it is unlikely that data on that combination can be used to extrapolate the long-term safety of the combination of dextromethorphan and bupropion. The dextromethorphan exposure is considerably higher when DM is combined with bupropion than when it is combined with quinidine, so the safety data in the Nuedexta database may underestimate the safety risks of the level of DM exposure that will occur with chronic use of AXS-05. In addition, the safety profiles of bupropion and quinidine individually are very different, posing a challenge for parsing the effects of DM from the second drug in the combination products. Instead of trying to assess the safety of AXS-05 indirectly through the review of safety data on related products, we believe that the most appropriate plan is to directly assess the safety of AXS-05 by continuing to build the AXS-05 safety database until it reaches the number of patients recommended by the ICH E1 Guideline.*

Discussion: *The Sponsor asked whether patients who have not participated in a previous AXS-05 trial could enroll directly into the planned open-label trial. The Agency responded that this would be acceptable, as long as the protocol includes a minimum six-week lead-in treatment period for de-novo patients and enrolls only AXS-05 responders into the open-label treatment period. The Agency also clarified that both MDD and TRD patients can, and should, be included in the safety database.*

2.4. Clinical Pharmacology Questions

Question 9: Axsome has conducted single and repeat dose PK studies of AXS-05 in healthy volunteers under fasted conditions, examining the PK of each moiety, and comparing the PK to the reference listed drugs. Axsome also intends to conduct a food effect PK study of AXS-05. In

addition, Axsome intends to reference the PK information for specific populations and the clinical drug interaction information in the FDA package inserts for the following bupropion- and DM-containing products in support of our planned NDA filing: Wellbutrin, Wellbutrin SR, Wellbutrin XL, and Zyban (bupropion HCl); Aplenzin (bupropion HBr); Contrave (naltrexone HCl and bupropion HCl); and Nuedexta (dextromethorphan HBr and quinidine sulfate).

Does the Division agree that the completed pharmacology studies with AXS-05, the planned food effect PK study of AXS-05, together with the information from the FDA package inserts for the above bupropion- and DM-containing products will be an adequate package of clinical pharmacology studies to support an NDA filing?

FDA Response to Question 9: *Please note that if you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you should identify each listed drug in accordance with the Agency's regulations at 21 CFR 314.54. Furthermore, you must establish a "bridge" (e.g., via comparative bioavailability data) between your proposed product and* ***each*** *listed drug on which you propose to rely to demonstrate that such reliance is scientifically justified.*

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 on which an applicant relies. For additional information on the 505(b)(2) regulatory pathway, please see section 3.0 of this document.

We may be able to provide more concrete advice if you were to clarify on what information you intend to rely from each of the products you list here. For instance, it is not clear to us what information from Contrave or Nuedexta would be applicable to your product or how you would propose to bridge to those products.

Please also note that some properties are unique to the combination product itself (e.g., drug interaction potential, PK in specific populations), and that information cannot be borrowed from your selected reference listed drug(s). Therefore, in addition to what you have completed and planned, the following studies need to be included in your development program to inform proper labeling in the future:

- *Drug interaction potential between the individual components of your combination product;*
- *Relevant drug-drug interaction studies with co-administered medications;*
- *PK in specific populations (e.g., CYP2D6 poor metabolizers, hepatic impairment, renal impairment);*
- *TQT study*

Discussion: *At the Sponsor's request for clarification, the Agency agreed that the PK interaction between DM and bupropion was well characterized based on three completed PK studies. Additional drug-drug interaction studies of the DM/bupropion combination with*

other drugs should be conducted and PK of each component should be evaluated. The Sponsor plans to submit protocols for the Agency to review and provide feedback.

Additional Comments from Controlled Substance Staff

1. *Drugs that affect the central nervous system (CNS), are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential.*

   AXS-05 is a combination product formulated with two CNS-active drugs that activate receptors linked to abuse-related effects and drugs that are abused. Therefore, we recommend that you characterize the abuse potential of the combination product AXS-05. For information on the type of information and studies used to evaluate the abuse potential of a product we direct you to the Guidance for Industry: Assessment of Abuse Potential of Drugs (2017).

2. *You may include with your future IND submission a discussion of any data relevant to the abuse potential assessment for your product as well as your plans to collect additional data, in accordance with the above referenced guidance.*

3. *You will need to conduct nonclinical and clinical assessments of possible withdrawal and dependency by AXS-05. A clinical assessment of physical dependence and withdrawal should be conducted at the conclusion of a planned clinical study.*

4. *You should monitor and report all CNS or abuse-related AEs from your clinical studies with AXS-05 and provide detailed narratives for these AEs as recommended in section V.B. of the 2017 Guidance mentioned above. Also, you should provide the list of terms that prompt these reports (including abuse-related AE terms such as euphoria, attention, mood, psychomotor effects, inappropriate affect, patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases). Where narratives are provided, they should include time of onset, and duration of the event, dose of drug taken, severity, and outcome. If available, pharmacokinetic values for each individual subject who experienced these AEs should be provided to understand if there is a temporal correlation between drug plasma levels and AEs.*

5. *If applicable, you should also report all possible cases of abuse (subjects taking the drug for nontherapeutic purposes, e.g., for psychoactive effects such as high or euphoria) occurring in your clinical trials. In such cases, information collected by the investigator should include explanations from the subjects when there are drug accountability discrepancies. Towards this end:*

i. *Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials. These data should include study number, and type of study, subject ID number, narratives, case description, and details.*

ii. *Provide narratives for cases where the patients drop out from studies for reasons that might be coded as "protocol violation," "lack of efficacy" (to capture aberrant behavior in patients who drop out of the study supposedly due to lack of efficacy), "lost to follow up," "non-compliance to study medication or procedures," "over compliance," or for "other." Case reports should be provided separately.*

iii. *Report any use of the investigational formulation by individuals other than the patients (family member, health care practitioner, etc.).*

6. *CSS is available to review any animal or human dependence-related protocols prior to the initiation of studies.*

Discussion: *CSS mentioned the high dextromethorphan plasma levels produced in humans following the administration of the combination product and the possibility of the Sponsor needing to conduct a human abuse potential (HAP) study. CSS recommended that the Sponsor justify with supportive data whether a HAP study is or is not needed as a part of their abuse potential assessment of the combination product, AXS-05. Also, CSS reiterated to the Sponsor that they could submit abuse-related protocols (nonclinical and clinical) to the Agency for review and recommendations prior to beginning such studies.*

The Sponsor made note of the inability thus far to produce dextromethorphan plasma levels in rats that are comparable to the plasma levels of dextromethorphan reported in humans when given the combination product. The Sponsor stated that using mice may be an option instead of using rats if they conduct nonclinical abuse-related studies (i.e., drug dependence/withdrawal, drug discrimination and self-administration studies). They agreed to forward draft protocols to the Agency to be reviewed and will consider conducting a HAP study and provide justifications supporting their position of either conducting or not conducting a HAP study.

3.0 OTHER

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-

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

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

PRESCRIBING INFORMATION

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your

pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

DATA STANDARDS FOR STUDIES

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

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

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data

standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. 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.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

ABUSE POTENTIAL ASSESSMENT

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

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

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

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

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

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

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

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

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

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No issues requiring further discussion.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor response document.

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

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