# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211448Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119610

**MEETING MINUTES**

CMG Pharmaceutical Co., Ltd
C/O: Camargo Pharmaceutical Services, LLC
Attention: Kristi Norris, PhD
Senior Scientific and Regulatory Manager
2505 Meridian Parkway, Suite 175
Durham, NC 27713

Dear Dr. Norris:

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

We also refer to the meeting between representatives of your firm and the FDA on February 5, 2018. The purpose of the meeting was to discuss the regulatory pathway and development program for Aripiprazole OSF.

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 Martin Yoon, Regulatory Project Manager at (240) 402-3911 or martin.yoon@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | B |
| **Meeting Category:** | Pre-NDA |
| **Meeting Date and Time:** | February 5, 2018 11:30 AM to 1:00 PM (EST) |
| **Meeting Location:** | 10903 New Hampshire Avenue<br>White Oak Building 22, Conference Room 1309<br>Silver Spring, Maryland 20903 |
| **Application Number:** | IND 119610 |
| **Product Name:** | Aripiprazole Oral Soluble Film |
| **Indication:** | Schizophrenia |
| **Sponsor/Applicant Name:** | CMG Pharmaceutical Co., Ltd |
| **Meeting Chair:** | Mitchell Mathis |
| **Meeting Recorder:** | Martin Yoon |

**FDA ATTENDEES**

| | |
|---|---|
| Ellis Unger, MD | Director, Office of Drug Evaluation I (ODEI) |
| Robert Temple, MD | Deputy Director, ODEI |
| Tiffany Farchione, MD | Deputy Director, Division of Psychiatry Products (DPP) |
| Bernard Fischer, MD | Clinical Team Leader (Acting), DPP |
| Gregory Dubitsky, MD | Clinical Reviewer, DPP |
| Hao Zhu, PhD | Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP) |
| Huixia Zhang, PhD | Clinical Pharmacology Reviewer, OCP |
| David Claffey, PhD | CMC Lead, Office of Pharmaceutical Quality (OPQ) |
| Ta-Chen Wu, PhD | Biopharmaceutics Team Leader, Division of Biopharmaceutics (DB) |
| Gerlie Gieser, PhD | Biopharmaceutics Reviewer, DB |
| Laura McGhee, PhD | Nonclinical Reviewer, DPP |
| Lolita White, PharmD | Team Lead, Division of Medication Error Prevention and Analysis (DMEPA) |
| Loretta Holmes, BSN, PharmD | Safety Evaluator, DMEPA |
| Phuong Nguyen, PharmD | Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE) |
| Monique Killen, PharmD | Regulatory Project Manager, OSE |
| Martin Yoon, PharmD | Regulatory Project Manager, DPP |

**Participating via Teleconference**

| | |
|---|---|
| Mitchell Mathis, MD | Director, DPP |

**SPONSOR ATTENDEES**

| | |
|---|---|
| Woo Ick Jang, MD, PhD | President, R&D, CMG Pharmaceutical |
| Aeri Kim, PhD | Associate Professor, CHA Medical University |
| Hyun-Tae Lim, PhD | Head, Formulation Research, CMG Pharmaceutical |
| John Kim, PhD | President (RA), Seoul CRO |
| K. Gary Barnette, PhD | Sr. Vice President of Drug Development, Camargo Pharmaceutical Services, LLC |
| Kristi Norris, PhD | Senior Scientific and Regulatory Manager, Camargo Pharmaceutical Services, LLC |
| Robert Kessler, PhD | Sr. Director of Analytical Development, Camargo Pharmaceutical Services, LLC |
| Lisa Crose, PhD | Scientific and Regulatory Specialist, Camargo Pharmaceutical Services, LLC |

**Participating via Teleconference**

| | |
|---|---|
| Marc Wiles, PhD | Vice President of Scientific and Regulatory Affairs, Camargo Pharmaceutical Services, LLC |
| Scott Cain, PhD | Director of Scientific and Regulatory Affairs, Camargo Pharmaceutical Services, LLC |
| William Salminen, PhD, DABT, PMP | Director of Scientific and Regulatory Affairs, Camargo Pharmaceutical Services, LLC |
| Loan Pham, PhD | Senior Pharmacokinetic Scientist, Camargo Pharmaceutical Services, LLC |
| Marcoita Gilbert, PhD | Research Scientist, Camargo Pharmaceutical Services, LLC |

## 1.0 BACKGROUND

CMG Pharmaceutical Co., Ltd (CMG) has developed an oral soluble film (OSF) immediate release formulation of aripiprazole, an atypical antipsychotic, that is designed to dissolve within seconds on the tongue and to be administered with or without water or food for the treatment of patients with schizophrenia.

The Division of Psychiatry Products (DPP) met with CMG regarding their development program in a pre-IND meeting on October 29, 2013. This meeting involved discussion of the 505(b)(2) regulatory pathway for this product, dissolution and stability testing, planned studies (including a bioavailability/bioequivalence (BA/BE) study and a food effect study), a biowaiver for lower strengths of the product, and recommendation of a usability study. The Division informed the Sponsor that the effect of drinking water on bioavailability should also be assessed and advised that the 10 mg strength could be used in the BE and food effect studies but justification was needed for not using the highest strength (15 mg).

CMG has conducted two Phase 1 studies: 1) a study of relative BA between Aripiprazole OSF and the Abilify tablets and the effect of water on the BA of Aripiprazole OSF and 2) a study of the effect of food on the BA of Aripiprazole OSF. Based on favorable study results, CMG now intends to file an NDA application for aripiprazole OSF under section 505(b)(2) referencing Abilify tablets.

CMG has requested this pre-NDA meeting to discuss and reach agreement with the Agency on the format and content of an NDA for aripiprazole OSF for the treatment of schizophrenia. Specifically, CMG would like to discuss and obtain agreement on:

- Confirmation that the 505(b)(2) regulatory pathway is appropriate for approval of the proposed Aripiprazole OSF product, including confirmation of the proposed LD
- Confirmation that previous agreements with the Agency are still in effect
- The adequacy of the referenced clinical pharmacology, clinical, and nonclinical information, in combination with the proposed drug development program, to support the NDA
- The adequacy of the CMC program
- Any concerns that the Division may have with regard to other filing issues specific to the referenced product

## 2. DISCUSSION

### 2.1. REGULATORY/MEDICAL

***Question 1:*** Based on the information provided in the meeting information package, will the Agency confirm that the 505(b)(2) regulatory pathway still appears to be the appropriate regulatory pathway for filing of the Aripiprazole OSF NDA?

***FDA Response to Question 1:*** *Based on the available information, the 505(b)(2) pathway appears acceptable. Information on the 505(b)(2) regulatory pathway can be found in section 3.0 of this document.*

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

***Question 2:*** Does the Agency agree with CMG's proposal to not integrate the adverse event data from the 2 Phase 1 studies and that these data can be summarized separately in Module 2 of the proposed NDA?

***FDA Response to Question 2:*** *We agree that the adverse event data from the two Phase 1 studies should not be pooled. These data can be summarized separately in Module 2 of the NDA.*

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

***Question 3:*** Does the Agency agree that no ISE and ISS are required and that the Sponsor's plan for presenting the efficacy and safety data in Module 2 is sufficient for NDA filing and review?

***FDA Response to Question 3:*** *We agree that no ISE or ISS is required. A summary of safety and efficacy data with the reference product in Module 2 is appropriate but full Clinical Study Reports for the two Phase 1 studies must be provided in Module 5 also.*

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

***Question 4:*** A table listing the key agreements reached between CMG and the Division throughout the development program is provided in Section 7.1.3 of this package.

**Does the Division agree that these agreements are still in effect?**

***FDA Response to Question 4:*** *The agreements pertaining to clinical issues are still in effect.*

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

***Question 5:*** Does the Agency agree that the dataset and format of the Phase 1 study data is sufficient and acceptable for NDA filing and review?

***FDA Response to Question 5:*** *The proposed format is acceptable, but the data sufficiency will be a matter for filing review. Also, please be advised that dataset files (.xpt and define.pdf files) for safety data from the two Phase 1 trials are required in Module 5 of the NDA.*

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

***Question 6:*** Will the labeling of Aripiprazole OSF be required to contain a Medication Guide?

***FDA Response to Question 6:*** *A Medication Guide tailored for patients with schizophrenia will be required. Also, please be advised that Sections 8.1 through 8.3 of labeling must conform to the requirements of the Pregnancy and Lactation Labeling Rule (PLLR).*

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

## 2.2. CLINICAL PHARMACOLOGY

***Question 7:*** Does the Agency agree that the Sponsor-conducted bioavailability (BA) studies (single-dose PK, effect of water administration, and food effect) in conjunction with

pharmacokinetic information in the approved labeling for the LD, Abilify, would be sufficient to support the clinical pharmacology section of the Aripiprazole OSF 505(b)(2) NDA and that no additional PK studies will be required?

***FDA Response to Question 7:*** *At this time, we do not anticipate a need for additional studies; however, this will be a matter of review when the NDA is submitted.*

*In addition, please provide your justification for why a single dose of two 15mg strips is anticipated to be equivalent to a single dose of 30 mg Abilify tablet. Also provide justification for other doses of OSF compared to Abilify tablet.*

> ***Discussion:*** *The Sponsor agreed to include their rationale for a scientific bridging between their OSF product and Abilify tablet at dose levels that are not tested in their studies when they submit the NDA application. They will also include their rationale for why different means of administration of two strips (i.e., sequential vs. simultaneous) are not expected to cause any significant clinical difference.*

***Question 8:*** Does the Agency agree that, based on equivalent aripiprazole Cmax and AUC following Aripiprazole OSF administration, a clinical bridge between Aripiprazole OSF and Abilify Tablets is established to allow reliance on the Agency's previous findings of safety and efficacy for the LD?

***FDA Response to Question 8:*** *On face, the approach appears adequate. However, whether the equivalence is established will be a matter of review.*

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

**Additional OCP Comments**

*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:*** *No further discussion.*

***Question 9:*** Does the Agency agree that the rationale for the proposed request for a biowaiver for the 5 mg and 15 mg dosage strengths is appropriate?

***FDA Response to Question 9:*** *Yes. To further support the biowaiver request for the non-biostrengths (5 and 15 mg), include also in the package the comparative disintegration data*

*using the biostrength (10 mg) as the reference product, as well as the comparative in vitro dissolution profile data generated using the final proposed QC dissolution method.*

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

## 2.3. CLINICAL

***Question 10:*** Does the Agency agree that no additional clinical safety or efficacy studies are needed to support the Sponsor's Aripiprazole OSF product NDA?

***FDA Response to Question 10:*** *At this time, it appears that no additional clinical safety or efficacy studies are needed; however, this will be a matter for review after NDA submission.*

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

***Question 11:*** Does the Sponsor's usability study satisfy the Agency's requirements regarding the demonstration of the ease of use of Aripiprazole OSF?

***FDA Response to Question 11:*** *It is premature to determine whether your usability study satisfies the need to demonstrate safe and effective use of the product. In addition, we do not consider ease of use in determining safe and effective use of a product. To better inform our review, we recommend that you conduct a use-related risk analysis (URRA). This will be required for filing your NDA. Please note that a comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.*

*If you determine that a Human Factors (HF) validation study is not needed for your product based on your URRA, submit your risk analysis and justification for not conducting a HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination. We require 60 days to review your URRA. Please plan your development program accordingly.*

***Discussion:*** *The Sponsor requested clarification on the request to perform a use-related risk analysis (URRA). The Agency explained that a URRA is needed because the documents submitted do not provide a clear description of the steps required in the use of the product, nor do they identify potential use errors and mitigation strategies. The Agency informed the Sponsor to use the instructions for use as a starting point to evaluate all the steps involved in the use of their product, the errors that users might commit on each step, the potential*

*negative clinical consequences of use errors, and mitigation strategies. The Agency reiterated that the Sponsor should submit the URRA and justification for whether a human factors validation study is needed to the IND for Agency review and concurrence.*

*During the meeting, the Sponsor stated they do not see any risk in this particular product as compared to any other oral dosage form; however, they know of other oral dosage form products used in this intended population. The Agency advised the Sponsor to incorporate this information in their URRA and/or justification for review and concurrence.*

*The Sponsor agreed to submit a URRA and justification. The Agency plans to review and provide feedback within 60 days.*

*For more information, please refer to our Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors.*

*Additionally, we have provided an example of a URRA in a tabular format to facilitate an efficient review:*

| Task No. | Task Description | Potential Use Errors | Description of Harm/Severity | Mitigation |
|---|---|---|---|---|
| 1.2 | Open pouch | User tears/cuts/damages film while opening foil | Part of film cannot be administered which may lead to underdosing | Product package labeling -visual cues for opening pouch |
| | | Unable to open pouch | Cannot access drug which may result in no dose. | Instructions for Use (IFU) includes clear description for how to open the pouch |

***Question 12:*** Does the Agency agree that these data are adequate post-marketing safety database information to support NDA filing?

***FDA Response to Question 12:*** *You have proposed to address the postmarketing safety of oral aripiprazole products by providing FAERS data for the 10 quarters prior to NDA submission,*

*which is one year prior to the last labeling update for Abilify tablets. Given the extensive marketing experience with aripiprazole, your proposal is adequate.*

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

## 2.4. NONCLINICAL

***Question 13:*** Does the Agency agree that the excipient levels in Aripiprazole OSF are acceptable and that no nonclinical evaluation of excipients is required to support the safety of the Sponsor's product in the NDA?

***FDA Response to Question 13:*** *Yes, we agree.*

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

***Question 14:*** Does the Agency agree that no additional nonclinical testing is required to support the nonclinical safety of CMG's product to be submitted using the 505(b)(2) regulatory pathway?

***FDA Response to Question 14:*** *We agree that no additional nonclinical studies are required to file the NDA. However, as stated at the pre-IND meeting (10/29/2013), any difference in PK and/or safety concerns that may arise during development may need to be investigated in nonclinical studies.*

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

## 2.5. CMC

***Question 15:*** Will submission of 24-month stability data for Aripiprazole OSF, collected under protocol, with subsequent submission of 36-month stability data during NDA review, demonstrating stability of all key quality parameters, targeting 36-month expiry dating, be sufficient for NDA acceptance for review?

***FDA Response to Question 15:*** *This approach appears acceptable. The inclusion of the 36-month time point in the determination of the expiry period will depend on the timing of its submission and the availability of resources to evaluate the data.*

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

***Question 16:*** Does the Agency concur with the Sponsor plan to demonstrate similarity of the Aripiprazole OSF product regardless of the polymorphic microcrystalline structure of the API in the film?

***FDA Response to Question 16:*** *Aripiprazole hydrate appears to have clinically significantly different aqueous solubility to anhydrous aripiprazole as evidenced by their respective use in Abilify Maintena and Abilify tablets. We expect that you will provide data to demonstrate that the polymorphic content of the registration and future commercial batches is predictable and adequately controlled. In particular, it will be critical to link the polymorphic content of these batches to the clinical batches at time of use in the clinic.*

*We expect that the drug product release and stability specification will include a fully validated test and acceptance criterion for polymorphic content. The acceptance criterion will need to be justified based on no significant difference in bioavailability compared to the batches used in the clinical trials and on no changes to drug product critical quality attributes (e.g. appearance, dissolution, etc.) through the drug product's expiry period.*

*We note that you propose to justify an acceptance criterion for aripiprazole* (b) (4) *content based on information in an FDA reviewer's public summary and, as such, are proposing to reference information in a FDA reviewer's public summary for support of safety and/or effectiveness of your proposed product. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. FDA reviewers' public summaries do not constitute full reports of investigations. See 21 CFR 314.430(e)(2). A 505(b)(2) applicant that seeks to rely on the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug.*

***Discussion:*** *The Sponsor stated that they recently tested the polymorphic composition of the clinical batch (PV1) and found that it contained the aripiprazole* (b) (4) *rather than an* (b) (4) *aripiprazole polymorphic form. The other registration batches (PV2 and PV3) contained what appeared to be mostly the* (b) (4) *aripiprazole polymorph. Although they began each drug product manufacturing process with* (b) (4) *aripiprazole drug substance, they state that they have identified a manufacturing step where this* (b) (4) (b) (4) *They propose that the commercial product will contain only the* (b) (4) *polymorphic form and that a commercial manufacturing process will be developed to ensure this. The Agency indicated that if they propose to take this route that they would have to ensure that they have definitive evidence of the polymorphic composition of the clinical lot (PV1), at its time of use in the clinic. The Sponsor stated that they did not test the polymorphic composition its time of use in the clinic, but they have data after 30 months' storage. Further, they have stability data from other batches which showed that the polymorphic composition did not change during storage. The Agency stated that they should provide these data and explanations in the NDA, while recognizing that* (b) (4) *of* (b) (4) *appears possible given the* (b) (4) *of the drug product and that the* (b) (4) *is likely to be the thermodynamically more stable form.*

*The Sponsor also stated that whether the* (b) (4) *or* (b) (4) *form is present in the drug product is not critical as they have data to demonstrate that the* (b) (4) *form undergoes polymorphic change to the* (b) (4) *during drug product disintegration/dissolution after*

*administration. The Agency stated that they were unaware of this occurring in other aripiprazole oral dosage forms, but that these data could be provided to support their NDA.*

*The Sponsor clarified that both polymorphic forms of the drug substance are present in the drug product as a* (b) (4) *rather than being dissolved in the dosage form.*

*The Sponsor asked whether a qualitative rather than a quantitative drug product polymorph content test would suffice, as the latter would be difficult to implement and validate. The Agency stated that this could be an acceptable approach for routine testing, if fully justified. The Agency expects that any justification will hinge on first having definitive quantitative polymorphic content of the clinical drug product batch at its time of use in the clinic.*

**Post-Meeting Comments**

1. *The acceptability of the indirect evidence of the clinical batch's polymorphic composition at the time of its use in the clinical studies provided will be a cross-disciplinary NDA review matter. If this evidence does not provide sufficient certainty of the polymorphic composition, additional studies may be requested (e.g., BE study of drug product formulated with 100% aripiprazole* (b) (4) *polymorph, etc.).*

2. *The use of* (b) (4) *aripiprazole and it* (b) (4) *to the aripiprazole* (b) (4) *in the manufacturing process could be an acceptable approach and will be an NDA review matter. We request that the NDA include a justification for relying on the manufacturing process to carry out a* (b) (4) *rather than beginning the process with the aripiprazole* (b) (4) *polymorph.*

***Question 17:*** Does the Agency agree with the Sponsor's plan to use a new Dissolution Test Method and that no additional stability testing will be required?

***FDA Response to Question 17:*** *At the time of NDA submission, we recommend inclusion of in vitro dissolution profile data (using the final proposed QC dissolution method) for at least 6 months of long-term stability testing of the primary registration batches, as well as supporting dissolution profile data for unexpired clinical trial lots. Submission of additional dissolution profile data in the 120-day Stability Update during NDA review is acceptable. However, the acceptability of the dissolution method bridging data will be determined at the time of NDA Review.*

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

**Additional Biopharmaceutics Comments**

*In the NDA, include data regarding the proposed QC dissolution method's (1) discriminating power for changes in quality attributes critical to dissolution including API polymorphic microcrystalline structure, and (2) stability indicating potential (if applicable).*

*Until such time that we are able to agree upon the dissolution acceptance criterion, FDA recommends collecting and reporting full in vitro dissolution profile data during stability testing. The dissolution data provided to support the stability of the proposed drug product should clearly specify whether the original or the final proposed QC dissolution method was used.*

***Discussion:*** *The Sponsor reported that the new in vitro dissolution method does not have the power to discriminate changes in API* (b) (4) *within the finished drug product. However, the new dissolution method is discriminating for changes in the film's* (b) (4) *composition.*

*FDA indicated that the Sponsor's proposed approach to establishing the adequacy of the proposed QC dissolution method appears reasonable, provided in the NDA the Sponsor successfully makes a case for the lack of clinical relevance of any API* (b) (4) (b) (4) *in the proposed to be marketed drug product during its manufacture and storage. FDA recommended that the Sponsor include in the dissolution method development report a list of the critical quality attributes of the drug product. FDA informed the Sponsor that other aripiprazole containing drug products have approved QC dissolution methods capable of showing dissolution profile differences between products with differences in API* (b) (4)

*Per the Sponsor, the dissolution sampling time points are 5, 10, 15 min, etc. FDA agreed that 5 min would be an appropriate initial sampling time point for dissolution testing of the proposed drug product.*

***Question 18:*** Is data from a single batch of the 5 mg, 10 mg, and 15 mg strengths sufficient to support the in vitro dissolution requirement for the biowaiver request in the NDA?

***FDA Response to Question 18:*** *To support the biowaiver request for the non-biostrengths (5 mg and 15 mg), provide comparative in vitro dissolution profile data for all the lots of the bio-strength (10 mg) used in the in vivo BE study, and three lots each of the non-bio-strengths (n=12 per lot). If dissolution is observed to change as a function of storage time, provide dissolution profile data for test and reference batches with comparable ages.*

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

***Question 19:*** Does the Agency agree that, in the event of any extractable/leachable impurities originating from the (b) (4) control at quality release of the product will be sufficient, with no further risk to be incurred during the product shelf-life?

***FDA Response to Question 19:*** *This approach is acceptable if you demonstrate that the drug product impurities method is capable of monitoring leachable impurities identified by extractable/leachable studies. Otherwise a specific leachables test will need to be developed and validated.*

***Discussion:*** *The Agency confirmed that the extractable/leachables will not need to be monitored in the drug product stability studies as the* (b) (4) *will be removed before drug product packaging. However, the leachables will need to be monitored in studies to support the* (b) (4)

## 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.

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.

## SUBMISSION FORMAT REQUIREMENTS

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

## ABUSE POTENTIAL ASSESSMENT

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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

## 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 following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators

who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

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

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously

(e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

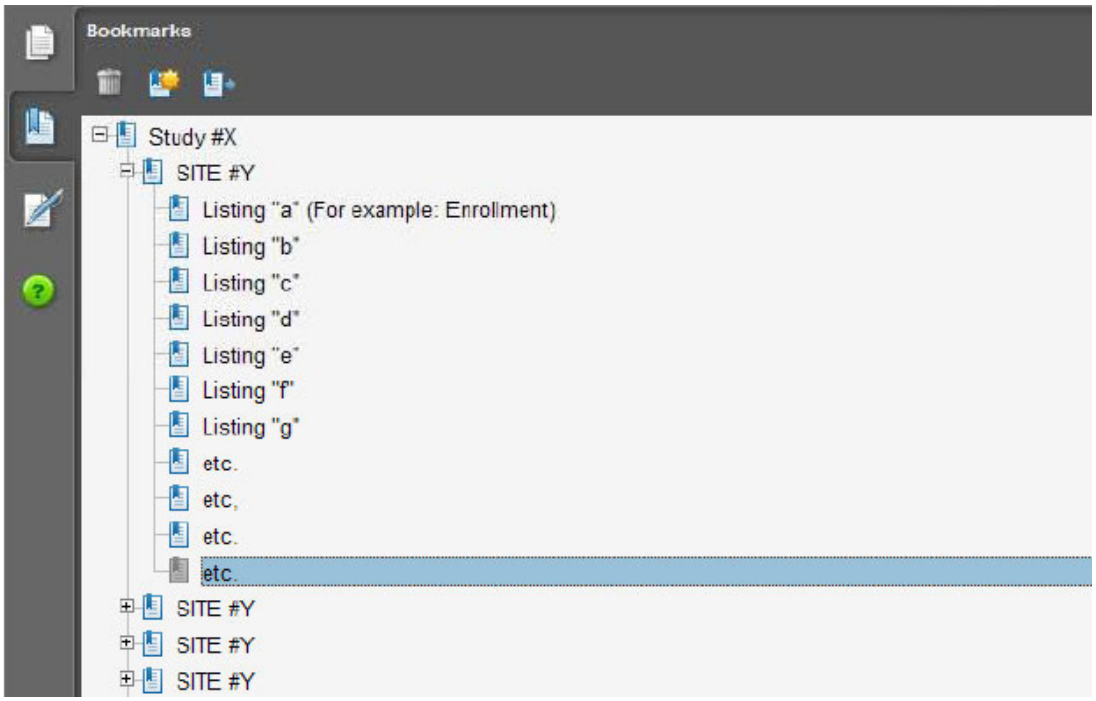
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

## II. Request for Subject Level Data Listings by Site

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

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




## III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf ) for the structure and format of this data set.

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

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

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

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


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

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

References:

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

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

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

## 4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

## 5.0 ACTION ITEMS

No action items were identified during the meeting.

## 6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

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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
03/05/2018