# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210875Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110955

**MEETING MINUTES**

Sunovion Pharmaceuticals Inc.
Attention: Sonya Roeloffzen
Director, Global Regulatory Affairs
88 Waterford Drive
Marlborough, MA 01752-7010

Dear Ms. Roeloffzen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for APL-130277.

We also refer to the meeting between representatives of your firm and the FDA on February6, 2018. The purpose of the meeting was to discuss the original new drug application (NDA).

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

If you have any questions, call Jack Dan, Regulatory Project Manager at (240) 402-6940.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD
Deputy Director
Division of Neurology 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 6, 2018 from 3:00 pm to 4:00 pm |
| **Meeting Location:** | White Oak, Building 22, Room 1309 |
| **Application Number:** | 110955 |
| **Product Name:** | APL-130277 |
| **Indication:** | Acute intermittent management of OFF episodes in patients with Parkinson's disease |
| **Sponsor/Applicant Name:** | Sunovion Pharmaceuticals Inc. |
| **Meeting Chair:** | Billy Dunn, MD |
| **Meeting Recorder:** | Jack Dan, RPh |

**FDA ATTENDEES**
Billy Dunn, MD, Director, Division of Neurology Products (DNP)
Eric Bastings, MD, Deputy Director, DNP
Nick Kozauer, MD, Associate Director, DNP
Gerald (Dave) Podskalny, DO, MPHS Clinical Team Leader, DNP
Kenneth Bergmann, MD, Clinical Reviewer, DNP
LuAnn Mckinney, PhD, Nonclinical Reviewer, DNP
Dan Berger, PhD, Chemistry Manufacturing Controls, Reviewer
Atul Bhattaram, PhD, Clinical Pharmacology Reviewer, DNP
Kun Jin, PhD, Statistical Team Leader
Junshan Qiu, PhD, Statistical Reviewer
Jack Dan, RPh, Regulatory Project Manager

**SPONSOR ATTENDEES**
Antony Loebel, MD, Executive Vice President, Chief Medical Officer, Head of Global Clinical Development
Bradford Navia, MD, Senior Director, Global Clinical Development
David Blum, MD, Head, Global Clinical Research Neurology
Diana Hughes, MD, MSc, Head PVRM & Head Global PV
E. Radford Decker, PhD, Senior Director DMPK
James Rawls, PharmD, Head, Global Regulatory Affairs
Jane Xu, PhD, Head, Global Data Science
Kenneth Sciarappa, PhD, Senior Director, Global Data Science, Biostatistics

Kimberley Treinen, PhD, Executive Director & Head of Preclinical
Parul Bhargava, PhD, Associate Director, Global Data Science, Biostatistics
Paul McGlynn, PhD, Executive Director, Global Project Management
Rachel Morrison, GRSC, Associate Director, Global Regulatory Affairs
Renee Carroll, MS, RAC, Senior Director, Global Regulatory Affairs
Robert Goldman, PhD, Head Global Clinical Research & Medical Affairs
Sonya Roeloffzen Stokowski, MSc, Director, Global Regulatory Affairs
Thierry Bilbault, PhD, Head, Technical Operations
(b) (4)
Yu-Yuan Chiu, PhD, Senior Director, Clinical Pharmacology

## 1.0 BACKGROUND

Sunovion Pharmaceuticals Inc. (Sunovion) is developing APL-130277 (apomorphine hydrochloride) sublingual film for the acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (PD)

APL-130277 is a (b) (4) film strip of apomorphine for sublingual (sl) administration which is designed to deliver apomorphine systemically through absorption from the oral cavity mucosa, thus bypassing the extensive first pass metabolism associated with gastrointestinal absorption of the compound.

APL-130277 was developed by Cynapsus Therapeutics (Cynapsus) under Investigational New Drug application (IND) 110,955. Sunovion acquired Cynapsus on October 21, 2016.

APL-130277 obtained Fast Track designation on August 25, 2016.

Sunovion will submit a 505(b)(2) NDA for APL-130277 which contains the same active ingredient in NDA 021264 Apokyn injection.

FDA sent Preliminary Comments to Sunovion Pharmaceuticals Inc. on February 1, 2018.

## 2. DISCUSSION

**Question 1:** Integrated Efficacy Analysis: Sunovion proposes to submit a Summary of Clinical Efficacy (SCE) that will also meet the statutory requirement for an Integrated Summary of Effectiveness (ISE) for the reasons provided below. Does the Division agree with this proposal?

**FDA Response to Question 1:**
Yes, it is possible to submit the narrative portions of the SCE summarizing APL-130277 efficacy (including all subgroup analyses) within Module 2. The texts should contain functioning hyperlinks to the information found in the appendices, tables, figures, listings, and datasets for the ISE.

All appendices must have a hyperlinked table of contents (TOC) that uses logical names that describe its contents. If an appendix contains subsections, the TOC for the appendix should contain hyperlinks or bookmarks to each subsection. Create a Master TOC that lists the order and title of each of the appendices. The Master TOC should contain functioning hyperlinks or bookmarks that bring the reader to the location of each appendix listed. The SCE needs to be clearly labeled and navigable.

**Meeting Discussion:**
None.

**Question 2:** Clinical Development: Does the Division agree that the clinical development package as described below is sufficient to support a substantive review of APL-130277 (apomorphine hydrochloride) sublingual film 505(b)(2) NDA?

**FDA Response to Question 2:**
The clinical pharmacology and clinical trial information appear, on face, to be sufficient to support a review of your product. However, this will be a matter of review after your complete application is submitted.

We remind you that in order to rely on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate and establish a satisfactory "bridge" between your proposed product and the listed drug to be relied upon. You propose to rely on Apokyn (NDA 21264) and to justify such reliance through a comparison of your proposed product and APO-go. The acceptability of such an approach will be a matter for review and will depend on several factors, including, as we have previously noted, your ability to assure us of the "sameness" of the current Apokyn and APO-go products. Please refer to the following guidance for further information on the requirements for establishment of effectiveness of your product: "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products"
https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-ggen/documents/document/ucm072008.pdf

**Meeting Discussion:**
The Division's suggested including in the NDA the final results from Study 203, a comparative bioavailability study assessing Apokyn, Apo-go and APL-130277, because the information from the study may help with bridging Apokyn to APL-130277.

**Question 3:** Integrated Summary of Safety (ISS): Sunovion proposes to summarize the individual study level data from Studies CTH-203 and CTH-302 separately within the ISS given that these are ongoing studies with only a small number of subjects enrolled at the time of NDA submission and their differences in study design. Does the Division agree with this proposal?

**FDA Response to Question 3:**
Yes, we agree with your plan not to pool the available safety data from ongoing crossover design Study CTH-203 and proposed Study CTH-302. If your bridge to the reference drug (Apokyn) relies on the results of Study CTH-203 (a single dose, relative bioavailability study comparing the PK properties of APL-130277 with APO-go and Apokyn), you will need to include the final study report in the NDA.

As indicated by the advice letter of May 26, 2017, your NDA submission must include safety information from at least 100 patients treated with dosages of APL-130277 intended for clinical use for 6 months or longer, with at least half treated with the highest recommended dose. Additional safety data from ongoing long-term safety studies should be submitted in the 120-day safety update.

Due to the titration and flexible dosing design of your pivotal trial, CTH-300, please include a table of adverse events for the actual dose received by the study period (i.e., titration versus maintenance) for all subjects, and a separate table for subjects who had a dose reduction any time during the trial. Please also see our response to Question 1 regarding the need to ensure the navigability of the ISS in the same manner as the SCE.

**Meeting Discussion:**
FDA recognized that in the pivotal clinical trials, APL-130277 was administered using a flexible and intermittent dosing schedule, so that the requirement for having information from at least 100 patients treated with dosages of APL-130277 intended for clinical use for 6 months or longer, with at least half treated with the highest recommended dose, does not directly apply. FDA stated that dosages described in labeling would need to be supported by the clinical trials (controlled and long-term) experience. The Sponsor should provide a clear and unambiguous presentation of the doses (mg) used, the number of doses taken each day, and for how many days each dose was used in the submission. The Sponsor clarified that the number of doses taken each day by each patient can only be inferred and calculated from the number of doses dispensed at each visit and the number of doses returned at the following visit. The dose and frequency of administration is only available from patient diaries kept for the two-day period prior to scheduled study visits.

FDA suggested that diary information from the two days prior to each visit be provided to support the maximum daily dose and frequency of administration described in labeling (i.e., mg dose x number of times taken in each day).

The Sponsor is encouraged to present the experience supporting the use of APL-130277 in ways that show the varied patterns of use among individuals but clearly indicate how adverse events are related to dose and method of use. This information should also be identifiable in the datasets for review.

The Sponsor stated their intent to present the results of the thorough QT study to provide some reassurance for cardiac safety, especially at higher doses.

The Sponsor should make clear in both in datasets and adverse event reporting at what exposure common events, such as nausea and vomiting and orthostasis, take place. The use of domperidone should also be "flagged" in both the datasets and reports with the understanding that domperidone, a medication not approved in the US, is also not available for use in the label. An analysis and discussion should be provided to assess whether the concomitant anti-emetic use may have affected the observed side-effect profile.

**Question 4:** Nonclinical: Sunovion has conducted a 3-month apomorphine sulfate rat toxicology study to confirm the safety of the Phase II conjugate apomorphine sulfate metabolite. Sunovion will submit an audited draft report (without SEND datasets) for the 3-month apomorphine sulfate rat toxicology study in the original NDA. Does the Division agree?

**FDA Response to Question 4:**
Nonclinical studies needed to support approval must be provided as final study reports at the time of NDA submission (see Written Responses, May 26, 2017).

If you are not able to rely on other sources to support the safety of your proposed product (see the comments in our response to Question 2), you will need to provide data from a full battery of nonclinical studies to support an NDA (see ICH M3(R2), January 2010; ICH M3(R2), February 2013)

**Meeting Discussion:**
None.

**Question 5:** Priority Review: Does the Division have any comments regarding the proposed outline of the information Sunovion will provide to support a request for Priority Review of the APL-130277 (apomorphine hydrochloride) sublingual film NDA?

**FDA Response to Question 5:**
Review status is decided after the application is submitted.

**Meeting Discussion:**
None.

**Question 6:** Office of Scientific Investigation (OSI) Information: Sunovion proposes to submit the necessary OSI information for Study CTH-300 given the study objectives and design and that it meets the requirements of a major trial used to support safety and efficacy in the application. Does the Division agree with this proposal?

**FDA Response to Question 6:**
In addition, submit the same information for open label extension study CTH-301.

**Meeting Discussion:**
None.

## 3.0 OTHER IMPORTANT INFORMATION

### PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A Sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

### 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.

## SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

## 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

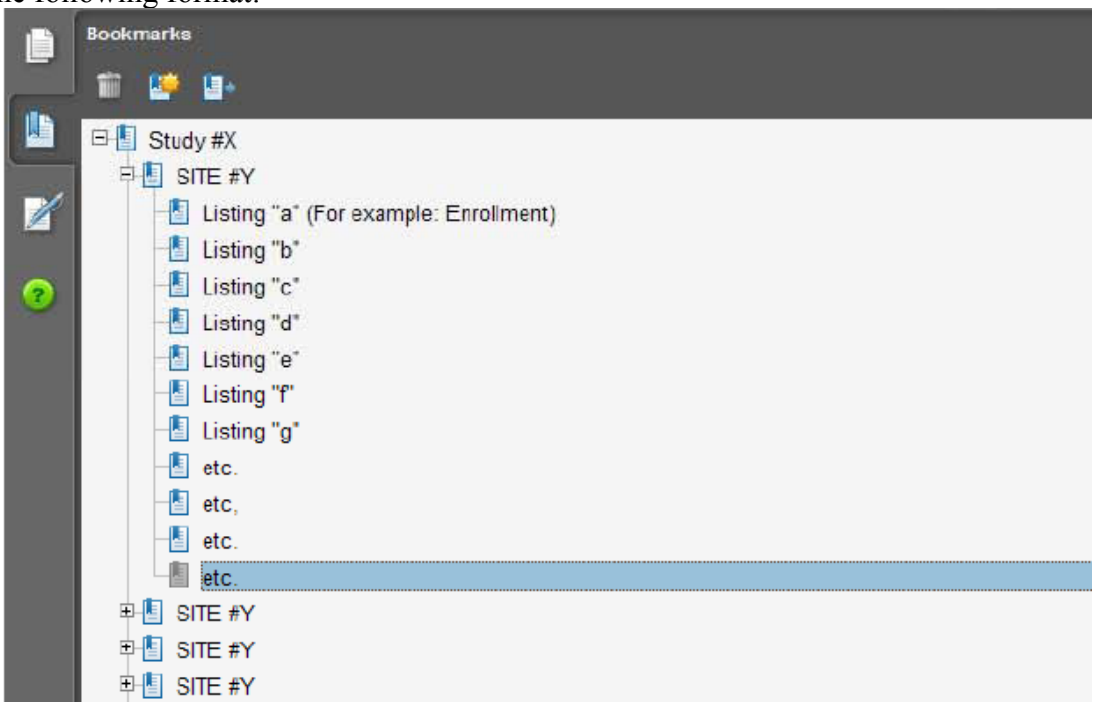
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which Sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

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


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

References:

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

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

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

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/s/

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ERIC P BASTINGS
03/07/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110955

**MEETING MINUTES**

Cynapsus Therapeutics, Inc.
Attention: Jordan Dubow, M.D.
Director of Medical Affairs
One Northbrook Place Center
5 Revere Drive, Suite 200
Northbrook, IL 60062

Dear Dr. Dubow:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apomorphine sublingual thin film (APL-130277).

We also refer to the meeting between representatives of your firm and the FDA on February 4, 2015. The purpose of the meeting was to discuss the Phase 3 development plan for the treatment of Parkinson's disease.

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

If you have any questions, call Tracy Peters, Senior Regulatory Project Manager at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

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

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | Type B |
| **Meeting Category:** | End of Phase 2 |
| **Meeting Date and Time:** | February 4, 2015; 11:00am-12:00pm EST |
| **Meeting Location:** | FDA White Oak |
| **Application Number:** | 110955 |
| **Product Name:** | apomorphine sublingual thin film (APL-130277) |
| **Indication:** | Parkinson's disease |
| **Sponsor/Applicant Name:** | Cynapsus Therapeutics, Inc. |
| **Meeting Chair:** | Billy Dunn, MD |
| **Meeting Recorder:** | Tracy Peters, PharmD |

**FDA ATTENDEES**
Billy Dunn, MD, Director, Division of Neurology Products
Gerald David Podskalny, DO, MPHS, Clinical Team Leader
Kenneth Bergmann, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
LuAnn McKinney, PhD, Pharmacologist
Martha R. Heimann, PhD, OPQ/ONDP, CMC Lead
Salaheldin Hamed, PhD, OPQ/ONDP, biopharmaceutics reviewer
Angela Y. Men, MD, PhD, Clinical Pharmacology Team Leader
Ta-Chen Wu, PhD, Senior Clinical Pharmacology Reviewer
Kun Jin, PhD, OTS/OB/Biometrics I, Team Leader
Junshan Qiu, PhD, Statistical Reviewer
Venakatesh Atul Bhattaram, PhD, Pharmacometrics Reviewer
Irene Z. Chan, PharmD, BCPS, DMEPA, Associate Director
Danielle Harris, PharmD, BCPS, DMEPA, Team Leader
Justine Harris, RPh, DMEPA, Safety Evaluator
Antoine El Hage, MD, OSI, Medical Officer
LaShawn Dianat, PharmD candidate, Intern
Tracy Peters, PharmD, Senior Regulatory Project Manager

**SPONSOR ATTENDEES**
Anthony Giovinazzo, President and CEO
Albert Agro, PhD, Chief Medical Officer
Thierry Bilbault, PhD, Chief Scientific Officer

Jordan Dubow, MD, Medical Director
Bruce Dzyngel, Vice-President, Clinical Development
(b) (4)
Karl Kieburtz, MD, MPH, Professor, Department of Neurology, Center for Human Experimental
(b) (4)
Robin M. Walker, PhD, Preclinical Development
Jonathan Kirkwood, Regulatory Affairs

## 1.0 BACKGROUND

Apomorphine is a non-ergoline dopamine agonist. Apokyn (apomorphine 10mg/ml administered via injection) is indicated for the acute, intermittent treatment of "off" episodes (b) (4) associated with advanced Parkinson's disease. Cynapsus is developing a (b) (4) apomorphine film strip, APL-130277, to be administered sublingually as an adjunctive therapy for the on-demand management of "off" episodes in patients with Parkinson's Disease who experience motor fluctuations. Cynapsus intends to submit a marketing application, pursuant to section 505(b)(2) of the FDC Act, that references Apokyn. Previous discussion of the APL-130277 development plan occurred on April 20, 2011, in a Pre-IND meeting between Cynapsus and the Division. In a letter dated October 23, 2014, the Sponsor requested an End-of-Phase 2 meeting to discuss the Phase 3 development plan, including the planned pivotal efficacy study (CTH-300), long-term safety study (CTH-301), and a bioavailability/bioequivalence study (CTH-200).

On January 5, 2015, the Division received the Sponsor's meeting package, which included the background information and meeting questions. The Agency's preliminary responses to those questions were electronically communicated to the sponsor on February 2, 2015. The following section is an account of the meeting questions, responses and the meeting discussion.

## 2.0 DISCUSSION

### 2.1. Clinical

***Sponsor's Background for Clinical Question 1:***
*Efficacy approach vs bioequivalence for 505(b)(2)*
*Cynapsus' APL-130277 shows a similar PK profile to subcutaneous apomorphine however, differences in t½ and AUC compared to the RLP (APOKYN) strongly suggest that the efficacy and safety of APL-130277 will be improved. A supra-proportional AUC and a longer t½ result in a smoother PK curve with milder side effects and sustained exposure in healthy volunteers. In patients, it results in a rapid improvement in motor function that is sustained substantially longer than the RLP with a side effect profile that appears less intense than the RLP. Based on these findings, Cynapsus feels that a pivotal efficacy program with a long-term safety extension is suitable for approval.*

***Clinical Question 1:***
***Do you still concur that the proposed pivotal registration program based, in part, on demonstrating efficacy of APL-130277, is the appropriate recommended approach for this 505(b)(2)-based submission?***

**FDA Response to Clinical Question 1:**
Please see our comments in the April 20, 2011, Pre-IND meeting minutes regarding the need for clinical information, the population in your Phase 3 clinical studies, the ability to rely on previous findings by the FDA and the ability to rely on information for the referenced listed product. Your plan to submit a 505(b)(2) NDA is acceptable. Whether the data are adequate to support NDA filing is a matter for review.

**Discussion:**
No further discussion.

***Sponsor's Background for Clinical Question 2a:***
*Study Design*
*The following studies are planned to demonstrate the efficacy, safety and tolerability of APL-130277:*

***CTH-300 Study:*** *A Phase 3, Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study to Examine the Efficacy, Safety and Tolerability of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations. The CTH-300 study will primarily assess the efficacy of APL-130277 as an on-demand therapy for the treatment of "OFF" episodes in levodopa responsive patients with Parkinson's disease who suffer at least 2 hours of "OFF" time during the waking period of the day and experience at least one "OFF" episode per day.*

***CTH-301 Study:*** *An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations. The CTH-301 study will primarily assess the long-term safety of APL-130277 as an on-demand therapy for the treatment of "OFF" episodes in levodopa responsive patients with Parkinson's disease who suffer at least 2 hours of "OFF" time during the waking period of the day and experience at least one "OFF" episode per day.*

***Clinical Question 2a:***
***Do you concur that the CTH-300 and CTH-301 studies, provided the anticipated outcome is achieved, are sufficient to demonstrate the efficacy and safety of APL-130277 as an adjunctive, for the management of "OFF" episodes?***

**FDA Response to Clinical Question 2a:**
The clinical trial synopses do not provide sufficient detail to fully determine their adequacy.

We are concerned about the ability to maintain blinding of treatment assignment in study CTH-300. The patient's experience with Apokyn prior to enrolling with APL-130277 in the Dose Titration Phase will likely make it possible for patients to discern which treatment arm

they have been assigned to, based on the difference in taste, tongue sensation and effect on their Parkinson's disease. A demonstration of dose-response by adding a low dose arm of APL-130277 may help to address that concern.

In order to provide a robust safety profile for a representative population of PD patients likely to receive APL-130277, we remind you that the trial should include apomorphine-naïve patients.

Study populations should be clearly defined and correspond to the specified data analyses. The intent-to-treat population, which includes all patients who are randomized and receive at least one dose of investigational product, should be the primary population for the primary analysis. The mean change from baseline is assessed only in patients with a baseline and a post-baseline measurement. Therefore, imputation of missing values at baseline by the site-specific average is not acceptable.

Alternative approaches based on different assumptions for missing data should be proposed as sensitivity analyses. A strategy for pooling of low enrolling study sites should be pre-specified.

Please provide more details describing the closed-testing procedure for assessing the onsite time and duration of drug effect over the post-dose period. To strongly control overall type-I error in testing the primary, co-primary (if any), and key secondary endpoints, adjustment for multiplicity should be implemented in the analyses.

The proposed sample size was calculated based on the mean effect size estimated using the data from the literature. We recommend using the smallest effect size to calculate the sample size instead.

**Discussion:**

Cynapsus believes that the treatment blind is maintained by close matching of the placebo to the active drug product and that attenuation of the dopaminergic effects (especially nausea and vomiting) should occur during the titration phase. A very robust clinical effect of the drug may lessen concerns about the potential effect of any lapse in blinding upon the trial. Subjects were unable to distinguish placebo from active drug product when this was tested during an earlier Phase 1 study. Cynapsus should submit the test methods and results with the Phase 3 protocol.

Successful maintenance of the study blind will be a review issue, as is usual for all pivotal drug trials.

***Sponsor's Background for Clinical Question 2b:***

*Efficacy Endpoints.*

*The effectiveness of APL-130277 is based on its on-demand relief of motor symptoms associated with "OFF" episodes in PD. To evaluate the efficacy of APL-130277 in patients with "OFF" episodes, a 12-week study with both in-office and at-home evaluations is*

*proposed. The primary endpoint is proposed to occur at the 12-week office visit using an evaluation of the UPDRS Part III Motor Score pre-dose (in the practically defined "OFF" state with last dose of PD medications no later than 10 PM the night prior) and post-dose at 15, 30, 45, 60 and 90 minutes. In particular, the change from pre-dose UPDRS III to 30 minutes post-dose compared to placebo will constitute the primary efficacy endpoint.*

***Clinical Question 2b:***
***Do you concur with this proposed primary efficacy endpoint for CTH-300 to support the approval of APL-130277 for the management of "OFF" episodes in patients with Parkinson's disease?***

**FDA Response to Clinical Question 2b:**
Yes, provided that a positive result on the change in the UPDRS, Part 3 is supported by the key secondary endpoint (percentage of patients with a patient-determined full ON response within 30 minutes at Visit 13). APL-130277 is being studied for its' ability to provide "on-demand therapy for the treatment of OFF episodes in levodopa responsive patients with PD"; however, numerical improvement from baseline on the UPDRS, Part 3 score assesses the motor symptoms of PD but does not assess clinically meaningful reversal of OFF episodes.

**Discussion:**
Either the old or new version of the UPDRS Part III motor scale may be used in the trial, but a single version of the scale should be used throughout the trial.

FDA agreed that a very robust change at 13 weeks from baseline in UPDRS Part III scores will support clinical effectiveness, but in the case of a less robust motor effect, the patient perception of the ON period becomes more important. The sponsor suggested that the ON and OFF state will be easily differentiated by the patient, but FDA expressed concern that some milder patients may not find it so clear-cut. In the presence of a lower but statistically significant response in UPDRS Part III, the key secondary measures become important in determining the clinical meaningfulness of the result. The complete version of the Phase 3 protocol needs to include the criteria investigators will use to determine that patents have achieved the "Full ON" state within 30 minutes of dosing. FDA asked the sponsor to include an unambiguous description of its plan to asses this outcome measure. FDA asked the sponsor to describe how it planned to handle missing data and if needed, the plan to adjust for comparison of multiple timepoints (later than 30 minutes) and how this fits within the overall plan to control the Type 1 error rate.

The Statistical Analysis Plan should have a clearly defined and prespecified single hierarchy for testing significance to control Type 1 error. Additional key secondary endpoints should be prespecified and included in a single hierarchical test to control the overall Type 1 error. The UPDRS time-response curve from 15 to 90 minutes for demonstration of the onset time and duration of the drug effect may be included in the Clinical Trials section of the label; however, all descriptions of data presented in the label are subject to review.

***Sponsor's Background for Clinical Question 2c:***

*Safety monitoring*

*The pivotal program will examine the following safety parameters throughout each study:*

- *ECGs*
- *Orthostatic blood pressure*
- *Adverse Events*
- *Laboratory assessments (including Vitamin B6)*
- *Physical examination with particular emphasis on a standardized oral examination.*
- *Suicidal Ideation*
- *Sleep attacks*
- *Impulse Control Disorders*

*In addition, a Data Monitoring Committee will be established at the beginning of the program to assess on-going safety evaluations (including OH and oral safety) throughout the CTH-300 and CTH-301 studies.*

***Clinical Question 2c:***

***Is the safety monitoring as outlined in the protocol as well as the DMC oversight sufficient for CTH-300 and CTH-301?***

**FDA Response to Clinical Question 2c:**

Yes. Please note that electrocardiograms should be recorded at the time representing Cmax. Please see the guidance regarding composition and operation of clinical trial data monitoring committees, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf

**Discussion:**

No further discussion but please also see the meeting discussion under Clinical Question 2d.

***Sponsor's Background for Clinical Question 2d:***

*Long-term safety data*

*Apomorphine has been available for over ten years with a well-characterized safety profile that is consistent from short-term (4-weeks) to long-term (over 1 year) studies.*

*Upon completion of the proposed phase 3 studies, a total of up to 206 patients will have 6-month safety data with up to 63 of these patients having 9 months of safety data.*

*As it pertains to oral irritation issues, Cynapsus completed a 28-day hamster study that demonstrated no local irritation issues from either a macro- or microscopic evaluations. In addition, data from post-marketing surveillance of Uprima as well as the European label for Uprima, strongly suggest that oral irritation is not a significant adverse event seen with this type of treatment. Given that the systemic exposure to apomorphine in APL-130277 is similar to that of apomorphine s.c. injection, the nature of adverse events seen should be comparable. Cynapsus therefore believes that a 6 month safety study of APL-130277 is sufficient to characterize the long-term safety profile of APL-130277.*

***Clinical Question 2d:***
***Is following 206 patients for 6 months and up to 63 patients for 9 months sufficient to ascertain any concerns regarding the safety for APL-130277?***

**FDA Response to Clinical Question 2d:**
Yes, unless unexpected safety findings are identified that may require further testing. Please note you cannot rely on safety and effectiveness findings described in a European drug label for Uprima in your submission to the FDA.

You will also need to perform a Thorough QT Study prior to submission of the NDA application.

**Discussion:**
The Post Marketing Commitment of the RLD's sponsor to perform a Through QT (TQT) Study is publically available information. If safety information concerning drug effect on QTc becomes available in the label of the RLD, it may be referenced in the 505(b)(2) NDA application. However, if the drug product has a different metabolic profile or results in a longer exposure or higher plasma levels in some patients than the RLD, a TQT study may still be required.

A supramaximal dose of APL 130277 is not yet defined and FDA suggested that healthy subjects may be able to tolerate a supramaximal dose of APL 130277 with modifications to the dosing regimen.

***Sponsor's Background for Clinical Question 2e:***
*Patient population – apomorphine exposure*
*In both the CTH-300 and CTH-301 studies, patients will enter with a background that is either naïve to apomorphine or they will have had experience with apomorphine but stopped for a reason other than systemic safety or lack of efficacy. In addition, patients presently using s.c. apomorphine will be allowed in the study as long as they have not taken a dose within 7 days of screening. Such patients will be re-titrated to dose with APL-130277.*

***Clinical Question 2e:***
***Do you concur with this proposed patient population for CTH-300 and CTH-301?***

**FDA Response to Clinical Question 2e:**
Yes, provided the study population is representative of the intended treatment population.

Repeated use of apomorphine may attenuate the nausea commonly associated with this drug and the trial design should take this into account.

**Discussion:**
No further discussion.

***Sponsor's Background for Clinical Question 2f:***

*Patient population – types of "OFF"*

*All "OFF" episodes result from a lack of available dopamine in the synapse. These episodes can be managed quickly and on demand by stimulating dopamine receptors effectively. Apomorphine can treat all types of "OFF" episodes* (b) (4) *The pivotal efficacy and safety program will assess the effect of APL-130277 on all types of "OFF" either during in office visits or at home.*

***Clinical Question 2f:***

***Do you agree with this approach to demonstrate efficacy?***

**FDA Response to Clinical Question 2f:**

Please see the response to Question 2a above. In study CTH-300, you plan to conduct in office evaluations of patients in a "functional off state" by withholding their morning Parkinson's medications. We anticipate that the indication would not specify which type of "OFF" the drug is indicated for.

**Discussion:**

No further discussion.

***Sponsor's Background for Clinical Question 2g:***

*Dosing Regimen*

*Cynapsus and its clinical experts feel that the dose titration used for the RLP is not commiserate with the safety data that has been established for apomorphine. While the pivotal program discussed herein will use a similar dosing titration to that of Apokyn, Cynapsus feels this may be modified based on the following:*

*a) Existing safety data as outlined in the literature,*
*b) the safety data originating from the pivotal efficacy study CTH-300,*
*c) the safety data originating from the long-term safety study CTH-301,*
*d) the consensus of the DMC,*
*e) a prospective, randomized peri-approval study that uses a modified dosing regimen.*

***Clinical Question 2g:***

***Do you agree that the dosing procedures may be modified post-approval based on safety data obtained from the each of the above?***

**FDA Response to Clinical Question 2g:**

No. The proposed dosing regimen needs to be supported by clinical data derived the safety and efficacy information from the controlled clinical trial experience included in your NDA submission. The consensus opinions of the DMC and literature reports are not empirical evidence that can support dosing instructions in the product label. Information from placebo controlled, randomized safety and efficacy studies conducted in the post-approval period can support change in the dosing information. However, you would need to submit this information as an NDA supplement that would require to FDA review.

**Discussion:**
Any modification of the CTH-300 and 301 trial protocol must be submitted to the IND as an amendment and should include a justification for the change.

***Sponsor's Background for Clinical Question 3:***
*BA/BE bridging study*
*CTH-200 Study: This study will be run with to-be-marketed clinical trial material and is designed to demonstrate the BA and BEQ between a single dose of APL-130277 and sub-cutaneous apomorphine in a cross-over design in healthy volunteers.*
*In general, the highest dose of test intended for use and reference product at the approved dose are used for such studies; however, given the known tolerability issues with Apokyn in healthy volunteers consistent with the labeled route of administration, Cynapsus proposes to use 2 mg subcutaneous doses of apomorphine to represent Apokyn injectable, for comparison to the 15 mg dose of* (b) (4) *film preparation. Two formulations of 15 mg APL-130277, the to-be-marketed formulation and the formulation used in the CTH-105 study, are proposed to be used in the study to provide a bridge between CTH-300 and earlier study results. The CTH-105 clinical material was produced on lab scale* (b) (4)

*This study will be completed in 36 healthy volunteers, as are BEQ/BA studies. As suggested in FDA's response to the pre-IND proposals, this study will extend the time points for sample collection out to 240 minutes. This study will also include a full assessment of metabolites from APL-130277.*

***Clinical Question 3:***
***Do you concur that the design of the CTH-200 is sufficient to bridge both the*** (b) (4) ***film formulations to each other and to the reference product APOKYN, and that the study can provide sufficient confirmatory information along with CTH-300 and CTH-301 to permit consideration for approval under 505(b)(2)?***

**FDA Response to Clinical Question 3:**

- Your proposed design seems appropriate to support the approval of the remaining strengths (10, 20, 25, and 30 mg) not included in the *in-vivo* bioequivalence study, but you should request a biowaiver for the remaining strengths. Your request should include the following supportive information:
  - **(1)** linearity of the pharmacokinetics over the therapeutic dose range,
  - **(2)** the remaining strengths are compositionally proportionally similar to the strength used in the in vivo BE study and,
  - **(3)** the dissolution profile data using 3 different pH media and mild testing conditions (*pH 1.2, 4.6, and 6.4; USP App 1 at 100 rpm or USP Apparatus 2 at 50 rpm*) should demonstrate similarity in the dissolution results between each tested strength and the reference strength used in the BE study.

- Yes, the proposed study is generally sufficient to bridge the (b) (4) film formulations and the reference product (Apokyn), if the "to-be-marketed formulation" is used in the proposed Phase 3 clinical trials. Otherwise, the "to-be-marketed formulation", the clinical formulation used in Phase 3 trials (if significantly different), and the reference product should be compared.

- You protocols should include a detailed description of how the (b) (4) film strips will be administered. If patients may swallow a portion of sublingual apomorphine dose, you should address the potential effects of orally ingested apomorphine, such as how extensive first-pass metabolism, food, (etc.) may influence the dosing regimen, and the clinical efficacy and safety during your drug development program.

  **Discussion:**
  The sponsor clarified that it will submit the PK results from the old formulation in labeling and remove the treatment arm with the old formulation from the proposed BA/BE study.

## 2.2. Chemistry, Manufacturing, and Controls (CMC)

***Sponsor's Background for CMC Question 1:***
*Stability protocol*
*The drug product, APL-130277, is a* (b) (4) *film that is designed to deliver apomorphine hydrochloride sublingually. The five different dosage strengths of apomorphine proposed to be marketed will be produced by* (b) (4)

***CMC Question 1:***
***Do you concur that stability for all five doses to be marketed can be confirmed with a stability study design that uses the highest and lowest dosage strength*** (b) (4) ***to bracket all the dosage strengths?***

**FDA Response to CMC Question 1:**
Given the number of product strengths proposed, we recommend placing at least one batch of the middle strength on stability. Also, we recommend including a 9 month time point for the intermediate storage (30°C/65% R. H.) stability condition.

We note that your stability protocol includes storage of the bulk roll (b) (4). We remind you that the expiration dating period for the finished product should be calculated based on the date of manufacture, which is based on input of the active ingredient.

**Discussion:**
No further discussion.

***Sponsor's Background for CMC Question 2:***
*Pyridoxine (Vitamin B6)*
*As presented in the APL-130277 IND, pyridoxine hydrochloride is* (b) (4) *excipient in the product. Because we do not intend to make* (b) (4) *claims around pyridoxine, we do not intend to report assay and impurities associated with the excipient.*

***CMC Question 2:***
***Do you concur with this position?***

**FDA Response to CMC Question 2:**
Pyridoxine may also (b) (4). Therefore, to support omitting an assay for pyridoxine content, we recommend that you provide data in your submission to demonstrate that reducing the amount of this excipient does not adversely impact product stability.

**Discussion:**
Pyridoxine (b) (4)

***Sponsor's Background for CMC Question 3:***
*Packaging integrity*
*Cynapsus intends to test the packaging as per USP<671> in order to characterize the moisture permeation and light transmission characteristics of the packaging.*

***CMC Question 3:***
***Do you concur that this is the appropriate approach to testing the packaging?***

**FDA Response to CMC Question 3:**
We concur.

**Discussion:**
No further discussion.

***Sponsor's Background for CMC Question 4:***
*Ease-of-use*

*Cynapsus is developing a protocol to evaluate the ability of Parkinson's disease (PD) patients to open the proposed primary packaging (i.e. foil pouch) and rate the product ''ease of opening'' and ''ease of use'' attributes, including film handling and self-administration under the tongue.*
*Patients*
*At least 4 patients for each film size (10, 15, 20, 25, 30 mg) will be enrolled. PD patients will be recruited and enrolled based on the following criteria:*

*1. Have a diagnosis of Parkinson's disease*
*2. Be responsive to dopaminergic treatment*
*3. Experience any of the following types of "OFF" episode* (b) (4)

*Patients will present to the study site on their normal Parkinson's disease medication regimen and will be trained on the use of APL-130277. After training, their next dose of medication will be withheld and they will be tested when they subjectively notice wearing off of their last dose of medication.*

*Testing*
*1) Ease of Opening will be assessed by:*

- *Effectiveness of opening – Complete opening of the sealed pouch without the need for external instruments*
- *Efficiency of opening - The time used to perform the opening of the packaging*
- *Satisfaction of opening – Patients will use a provided rating scale to assess freedom of discomfort, and positive attitudes towards the ease of opening of the package*

*2) Ease of use/Use of Administration:*

- *Each patient will be given one sample of the product and complete a full opening of the foil pouch*
- *Patient will retrieve film between fingers, identify the UP side of the film (marked side of the film) and apply the film under the tongue.*

*Patients will allow the film to remain under the tongue for two minutes before swallowing.*

***CMC Question 4:***
***Do you concur with this approach to testing methods and study design for ease-of-use?***

**FDA Response to CMC Question 4:**
The FDA generally does not require an ease of use study since "ease of use" is a subjective parameter that does not provide the necessary data to evaluate whether intended users can use your product safely and effectively. However, your proposed "ease of use" study does raise concerns for the FDA regarding whether this particular patient population is able to manipulate your proposed container closure to access the medication as well as to administer this product. To address these concerns, we will first need to see the results of your use risk analysis. Note that "ease of use" is a subjective parameter that should not be the primary focus of your development program. Instead your primary objective should be to provide

supportive evidence that the final user interface design is optimized for use, i.e., it is safe and effective when used by intended users, for intended uses, and expected use environments.

A use-risk analysis is a systematic evaluation of use-related risk. This use risk analysis should include a comprehensive evaluation of all the steps involved in using your product (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit, including critical tasks they might fail to perform, and the harm that would result. You 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. Ensure that the following are considered as you proceed with your use risk analysis:

- For patients requiring a dose that is achieved with more than one strip, improper dose errors will occur if the appropriate number of strips are not utilized or are not placed correctly in the mouth
- Not all patients may receive training in the real world
- Confirmation bias can impact use for participants that have previous experience with other similar devices
- Patients may not be the only end user group for your product
- Users may not hold the strip in place for a full (b) (4)

This use-related risk analysis will help you to determine the extent of which simulated use human factors studies are needed in your development program. Additionally, the use risk analysis should be used to inform the design of a human factors validation study protocol for your product if one is required. A human factors validation study should be conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm

To ensure your approach and methodology are acceptable, please submit your risk analysis and study protocol (if applicable) for review prior to study implementation for Agency review and comment. Please note that we will need 90 days to review and provide comments on your study risk analysis and protocol under the IND.

**Discussion:**

Cynapsus agreed to conduct a comprehensive use-risk analysis, as described in the preliminary response, to help determine the extent of which simulated use human factors studies are needed in the development program and to inform the design of a human factors validation study protocol for the product, if one is required.

FDA raised concerns about the significance of strip orientation during placement under the tongue (i.e., if the side with exposed drug is placed down instead of up) and the consequences of a strip being placed upside down. Preliminary data indicates that orientation of the strip under the tongue does not significantly change absorption of apomorphine. Cynapsus will need to confirm this result. If it is determined that orientation of the strip significantly changes absorption, it should be reflected in the use-risk analysis with development of an appropriate risk mitigation strategy. It is likely that a human factors validation usability study would be required in this circumstance.

***Sponsor's Background for CMC Question 5:***

*Impurities/Degradation product testing and qualification*

*At this stage, stability data are not available for product made with the new/optimized formulation and scaled-up manufacturing process. However, preliminary 3-month accelerated stability data on the laboratory batches of the new formulation indicate that there are two degradation products at the* (b) (4) *level of the parent peak. These were tentatively identified by LC-MS as* (b) (4) .

*Cynapsus is continuing to evaluate the APL-130277 sublingual drug product for impurities and degradation products. Some degradation products could eventually exceed the ICH qualification threshold of* (b) (4) *% in the marketed drug product, based on a proposed maximum human dose of 200 mg/day consisting of five 40 mg (2x20mg) doses. Nonclinical safety evaluation with respect to general toxicology according to ICH* (b) (4) *guidelines may be appropriate depending on the identity of the impurity/degradation product; whether they are also a metabolite of apomorphine; and availability of information in the public domain. If nonclinical evaluation is required, it is proposed that a 4-week long repeated dose toxicology study be conducted either in hamsters using the cheek pouch as the route of administration (including full clinical and anatomic pathology evaluations for systemic toxicity) or in rats using the oral gavage route of administration with apomorphine containing appropriate levels of the impurities/degradants. The oral gavage route of administration might be appropriate if it was deemed necessary to administer higher doses than is possible sublingually, since apomorphine-induced clinical signs are expected to be dose limiting when it is administered parenterally. Furthermore it is assumed from clinical data that most (about* (b) (4) *% or more in humans) of a sublingual dose of apomorphine ends up*

*in the gastrointestinal tract, so the oral gavage route would appear to be the more relevant to APL-130277 than parenteral administration.*

***CMC Question 5:***
***Do you concur with the proposed approach to qualifying the impurities in the drug product?***

**FDA Response to CMC Question 5:**
Impurities needing qualification should be assessed for genotoxic potential and in a general toxicology study in one species. For chronic administration, the toxicology study should be of 90 days' duration and test apomorphine using a clinically relevant route. If the clinical data demonstrate that >80% of a sublingual dose is swallowed, then an oral toxicology study may be appropriate. Justification should be provided for the species and route selected.

**Discussion:**
The sponsor proposed conducting a 90-day oral toxicity study in rat for any impurities requiring qualification. Justification will be provided for the species and route of administration selected.

## 2.3. Non-Clinical

***Sponsor's Background for Non-Clinical Question 1:***
*Toxicity testing of potential impurity/degradation products*
*With respect to evaluation of genetic toxicity/DNA reactivity of potential degradation products described in CMC Question 5, compliance with the principles described in the 2014 ICH M7 Guideline is planned. Identified actual and potential impurities/degradants will be evaluated in 2 complementary in silico (Q)SAR programs (one expert rule-based and one statistical-based) for informational purposes. It is anticipated that where an impurity/degradant is similar to apomorphine, the outcome of computational evaluations will likely be positive, since apomorphine was positive in bacterial mutagenicity (Ames) assays (as indicated in the US Apokyn label). However, further testing of such impurities/degradation products is not planned, since the Scope of Guideline section in ICH M7 states that: "there may be some cases where a drug substance intended for other (non cancer) indications is itself genotoxic at therapeutic concentrations and may be expected to be associated with an increased cancer risk. Exposure to a mutagenic impurity in these cases would not significantly add to the cancer risk of the drug substance. Therefore, impurities could be controlled at acceptable levels for non-mutagenic impurities." It is assumed that APL-130277 falls into such a category.*

*Potential concern regarding apomorpine-induced mutagenicity is further mitigated by the recent information, now included in the updated US Apokyn label (July 2014), indicating that apomorphine likely poses no significant risk for carcinogenicity based on the results from a traditional long term study in rats and a 26-week study in transgenic P53-knockout mice. An increased incidence of Leydig cell tumors in male rats at the highest dose tested was considered of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell tumors in rats are not relevant to humans. No increased tumor incidence was seen in female rats or mice. Therefore, to the extent that a*

*positive mutagenicity outcome in in-silico evaluations of an impurity/degradation product in the APL-130277 drug substance or drug product is due to a structural alert that is shared with apomorpine itself, there would likely be even further diminished concern regarding potential for carcinogenicity associated with that impurity/degradation product.*

*It is considered unlikely that any of the APL-130277 impurities and degradation products would fall into the high potency "cohort of concern" described in ICH M7 that would be expected to represent greater risk for carcinogenicity and merit stricter controls.*

***Non-Clinical Question 1:***
***Does FDA consider this to be an acceptable approach with respect to safety assessment of potentially genotoxic impurities and degradation products in APL-130277?***

**FDA Response to Non-Clinical Question 1:**
We agree with your plan to assess the safety of potential impurities/degradants in a manner consistent with relevant FDA guidances.

**Discussion:**
No discussion.

***Sponsor's Background for Non-Clinical Question 2:***
*Metabolites*
*Based on preliminary investigations conducted by Cynapsus to-date (see section 10.3.2), the primary metabolite following administration of APL-130277 is sulfated apomorphine, which is consistent with previous studies* (b) (4) *both sublingual and subcutaneous administration of apomorphine Cynapsus will conduct full characterization of the metabolite profile of APL-130277 and APOKYN using validated assays in CTH-200 study and monitor metabolite levels in a subset of patients in CTH 301. Assuming the metabolite profile of APL-130277 observed in these studies remains consistent with that of other apomorphine containing products, we do not intend to conduct further non-clinical testing.*

***Non-Clinical Question 2:***
***Do you agree that non-clinical testing to address the safety of the sulfate metabolite of apomorphine is not required?***

**FDA Response to Non-Clinical Question 2:**
If the metabolic profile of APL-130277 following sublingual administration in humans is similar to that of APOKYN at the maximum recommended daily dose, further nonclinical testing of any major human metabolite(s) will not be necessary.

Your proposal to characterize the metabolite profile of APL-130277 and APOKYN in CTH-200 study (BA/BE) and monitor metabolite levels in a subset of patients in CTH-301 seems feasible. However, our greater concern is that PK of APL-130277 and its major metabolite, especially at higher doses (i.e., 30mg and 45mg), have not been adequately characterized in healthy subjects or patients in Phase 1 and Phase 2 studies. In the absence of a PK study to

evaluate the PK profiles across the proposed dose range, you should consider characterizing the PK and metabolite profiles in the proposed pivotal Phase 3 trial (CTH-300).

The results from completed studies suggest differences in metabolism or metabolite levels between subcutaneous and sublingual routes of administration. You should adequately address any qualitative and quantitative similarity or difference in metabolic profiles between these two routes of administration as part of your NDA submission.

**Discussion:**
Planned PK data collection in the pivotal Phase 3 study is sparse. In order to evaluate clinical PK at adequate doses over a sufficient duration and to reduce adverse effects in healthy volunteers, Cynapsus proposed conducting a dedicated PK study in PD patients. The sponsor acknowledged the need to provide adequate justification as part of the NDA in the event that bioequivalence between TBM sublingual formulation and the reference drug product cannot be established.

To evaluate the risk of QT prolongation, FDA suggested that the sponsor collect time matched QT data and concentrations of apomorphine and its metabolite in the clinical trial (CTH-300). The risk of QT prolongation can be characterized by analyzing the relationship between changes in QT and concentrations of apomorphine and its metabolite. The sponsor should propose a detailed sampling schedule for review.

***Sponsor's Background for Non-Clinical Question 3:***
*Non-clinical development*
*Given there are no significant outstanding issues from nonclinical investigations to date, Cynapsus does not intend to conduct further nonclinical studies in support of the development of APL-130277, except if necessary to qualify impurities at noted above.*

***Non-Clinical Question 3:***
***Do you concur with this approach?***

**FDA Response to Non-Clinical Question 3:**
Provided impurity issues are adequately addressed, additional nonclinical studies may be needed only if there are excipients that raise safety concerns or if the metabolic profile for APL-130277 in humans indicates higher systemic exposure to one or more metabolites, compared to APOKYN.

**Discussion:**
The sponsor stated that apomorphine sulfate, the primary circulating metabolite in human, does not represent a safety concern. FDA agreed that additional safety testing of the metabolite is not necessary.

## 3.0 ADDITIONAL INFORMATION

### PREA REQUIREMENTS

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

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

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

### DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

### LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting

mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm ).

**505(b)(2) REGULATORY PATHWAY**

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

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

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

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

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

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

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

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

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

**Please note that "full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. SBAs, FDA reviewers' public summaries, and advisory committee materials 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 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.**

## 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

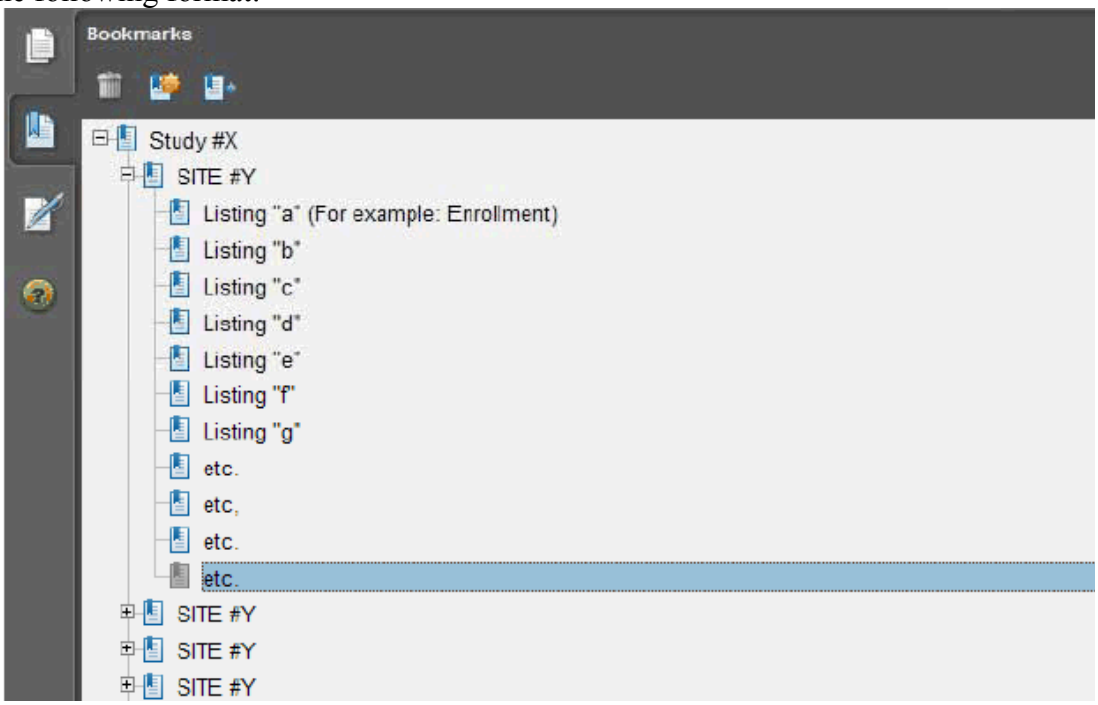
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

## 4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

## 5.0 ACTION ITEMS

None.

## 6.0 ATTACHMENTS AND HANDOUTS

None.

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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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WILLIAM H Dunn
03/03/2015