CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216264Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 137856

MEETING PRELIMINARY COMMENTS

Provepharm SAS
C/o Clinipace Inc.
Attention: Clara Li, MS
Vice President, Regulatory and Strategic Development
US Agent to Provepharm SAS
1434 Spruce St, Suite 100
Boulder, CO 80302

Dear Ms. Li:

Please refer to your pre-investigational new drug application (PIND) file for indigo carmine.

We also refer to your April 26, 2019, correspondence, received April 26, 2019, requesting a meeting to discuss the proposed protocol synopsis and to obtain feedback on the sponsor's responses to FDA meeting minutes dated January 30, 2019.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at 301-796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: June 18, 2019; 2:30 pm -3:30 pm ET
Meeting Location: White Oak Bldg 22. Conf. rm 5201/Teleconference

Application Number: PIND 137856
Product Name: Indigo Carmine

Indication: Indigo carmine is indicated for use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures

Sponsor/Applicant Name: Provepharm SAS

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 18, 2019, 2:30 pm- 3:30 pm ET, between Provepharm SAS and the Division of Medical Imaging Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On April 26, 2019 Provepharm SAS submitted a meeting request to the Division of Medical Imaging Products. The purpose for the meeting is to discuss the proposed protocol synopsis and to obtain feedback on the sponsor's responses to FDA meeting minutes dated January 30, 2019.

2.0 DISCUSSION

We have reviewed the meeting package submitted on April 26, 2019 and provide the following responses to the questions.

Question 1d(1):
As agreed at the 23 January 2019 meeting, Provepharm has updated the proposed clinical trial synopsis to include the following defined 3-point ordinal rating scale for ureter visualization (referred to as the 3-point Ureter Visualization Scale):
1= Not visualized – I cannot see the ureteral jet flow
2= Inadequately visualized or equivocal – I am less than completely confident that the ureter is patent
3= Adequately visualized or unequivocal – I am completely confident that the ureter is patent

Sponsor question: Does this satisfy the agency's request for the assessment scale?

FDA response to question 1(d)(1):
Yes, we agree.

Question 1d(2):
To evaluate the efficacy outcomes, each subject will first be injected intravenously with 5 mL 0.9% saline. The ureteral orifices/flow will be observed for up to 10 mins or until adequate visualization has occurred (whichever occurs first). This time period will be captured on video and the time from injection to adequate visualization will be recorded. The surgeon will rate his/her ability to visualize the ureteral jet stream indicating ureteral patency for each ureter according to the scale above. The process will be repeated in the same patient for the IC dose. The surgeon will be blinded to the IC dose a subject is given.

Each ureter will be rated independently using the 3-point ordinal scale as well as time to visualization. Hence, each subject will have 4 observations for ureter patency assessment and time to visualization assessment.

Sponsor question: We plan to analyze the treatment effect on the 3-point ureter visualization scale with Generalized Estimate Equation (GEE) for repeated measures. The model will include a repeated statement to account for intra-subject correction. Does the agency agree with this approach? If not please advise.

FDA Response to question 1d(2):
In general, the GEE approach appears reasonable. Please include model specification in the statistical analysis plan (SAP) for our review.

Question 1d(3):
The primary efficacy endpoint of the study will be the score rated by the surgeon using the 3-point ureter visualization scale. The scores from the blinded central reader will be analyzed using the same statistical analysis model as a sensitivity analysis;

The pattern of consistency/inconsistency between the surgeons and the blinded reader will be examined.

Sponsor question: Does the agency agree with this approach? If not, please advise.

FDA response to question 1d(3):
Yes, we agree that the primary endpoint would be the score rated by the surgeon using the 3-point UVS. Please perform the analysis of the 3-point UVS score as rated by the blinded reader. Additionally, please propose a method to examine the consistency between the surgeon and the blinded reader. How well the reading correlate will be a review issue.

Question 1d(4):
We agree that the surgeon will be blinded to the randomized IC dose a subject is given.

Sample Size Consideration
It is assumed that the IC treatment will improve the ureter visualization by 0.5 points or more comparing to the normal saline using the 3-point UVS measurement. A total of 96 subjects will be enrolled in the study; 48 subjects randomly assigned to 2.5 mL IC and 48 subjects assigned to 5.0 mL IC. This sample size calculation was determined based on two-group Chi-square test comparing proportions in 3 categories at 0.05 significance level.

The sample size does not account for drop outs, protocol deviations, withdrawal of consent, etc. Up to an additional 20% (20) subjects may be enrolled to account for protocol deviations, withdrawal of consent, etc.

Multiplicity

There are two null hypotheses for the primary efficacy endpoint (ureter visualization scale).

1) there is no difference between the IC high dose and the normal saline
2) there is no difference between the IC low dose and the normal saline

Multiplicity due to the two null hypotheses will be controlled by Hochberg method. Nominal p-values will be presented as is. To control family-wide Type I error to be less than or equal to 0.05, when both nominal p-values are less or equal to 0.05, both null hypotheses will be rejected and one will conclude that both IC dose groups are statistically different from the saline group in the examined parameter. When one of the two nominal p-values is greater than 0.05 but the second nominal p-value is less or equal to 0.025, the null hypothesis associated with the first nominal p-value is failed to be rejected and the null hypothesis associated with the second nominal p-value will be rejected. If the second nominal p-value is greater 0.025, the null hypothesis associated with the second nominal p-value is also failed to be rejected.

A formal Statistical Analysis Plan (SAP) will be developed for this study after the full protocol is written. The SAP will be sent to the agency for review and comments.

Sponsor question: Does the agency agree with this approach? If not, please advise.

FDA response to question 1d(4):
Please justify the association between the improvement on the ureter visualization by 0.5 points using the 3-point UVS measurement and the distribution of proportion of subjects in each of the three UVS categories. Also, clarify what method was used to calculate the effect size (b) (4) , e.g., Cohen, Hedges and provide the reference.

The statistical approach for controlling multiplicity is acceptable.

Question 1d(5):

It is planned to have a follow-up visit 7-30 days after the surgery for monitor safety; and a final telephone call will occur in subjects who have this follow-up visit prior to Day 28 after the surgery. At the follow-up visit vital signs, 12-lead ECG, and clinical laboratory tests will also be collected.

Sponsor question: Does the agency agree with this approach? If not, please advise.

FDA response to question 1d(5):
This approach is reasonable from a safety standpoint. Please provide the follow-up for those patients in whom ureteral patency was not visualized or poorly visualized.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS
For the Protocol PVP-19IC01, we recommend that you add additional plasma PK sampling timepoints within 20 minutes following Indigo carmine administration and remove the plasma PK sampling timepoints after 2 hours following Indigo carmine administration. Indigo carmine has a plasma half-life of 4.5 minutes. In case of renal function impairment, the average time of excretion can be extended for several minutes. Plasma PK sampling timepoints up to 2 hours should be adequate.

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-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.[1] 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 FDA.gov.[2]

4.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[4] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before

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[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[4] http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[9]

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[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Electro nicSubmissions/ucm174459.htm

[7] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[9] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

6.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[12] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[13]

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.

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[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[11] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf

[12] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[13] http://www.regulations.gov

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.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[14]

8.0 NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

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

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

9.0 UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

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

/s/

ALBERTA E DAVIS WARREN
06/13/2019 04:35:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 137856

MEETING MINUTES

Provepharm SAS
C/o Clinipace Inc.
Attention: Maureen Merrifield, PhD
Director Regulatory & Strategic Development
US Agent to Provepharm SAS
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

Dear Dr. Merrifield:

Please refer to your Pre-Investigational New Drug Application (PIND) file for indigo carmine.

We also refer to the telecon between representatives of your firm and the FDA on January 23, 2019. The purpose of the meeting was to discuss the adequacy of your proposed data package in support of a 505(b)(2) NDA application submission.

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

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
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 C
Meeting Category:	Guidance
Meeting Date and Time:	January 23, 2019; 3:00 pm - 4:00 pm ET
Meeting Location:	Teleconference/WO-22 Rm. 5270
Application Number:	PIND 137856
Product Name:	Indigo Carmine
Indication:	Indigo carmine is indicated as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures
Sponsor/Applicant Name:	Provepharm SAS
Meeting Chair:	Libero Marzella, MD, PhD
Meeting Recorder:	Alberta Davis-Warren

FDA ATTENDEES

Charles Ganley, MD, Director, ODEIV
Lesley-Anne Furlong, MD, Deputy Director, ODEIV
Libero Marzella, MD, PhD, Director, DMIP
Alex Gorovets, MD, Deputy Director, DMIP
Nushin Todd, MD, PhD, Clinical Team Leader, DMIP
Betsy Ballard, MD, FACS, Medical Officer, DMIP
Sue-Jane Wang, PhD, Acting Deputy Director, DBI
Ququan Liu, Primary Statistical Reviewer, DBI
Christy John, PhD, Clinical Pharmacology Team Leader, DCPV
Sam Habet, RPh, PhD, Clinical Pharmacology Reviewer, DCPV
Jagjit Grewal, MPH, Policy Advisor, OND Policy Staff
Carolyn Yancey, MD, Medical Officer, DPMH
Gettie Audain, DHSc, MPH, BSN, RN, APHN-BC, CAPTAIN, U.S.P.H.S./FDA/ Senior Regulatory Health Project Manager, DPMH
Hari Cheryl Sachs, MD, Team Leader (Pediatric), DPMH
Alberta Davis-Warren, RPM, DMIP

SPONSOR ATTENDEES
Mary Jane Helenek, Executive Vice President and Chief Operating Officer / Provepharm Inc
Marc Tokars, Consultant
Frederic Girard, Chief Medical Officer/ Provepharm SAS
Emilie Huyghues des Etages, Deputy R&D Director and Head of Innovation / Provepharm SAS
Kathleen C. Heil, RN, BSN, Director, Clinical Operations/ Provepharm SAS
(b) (4)
Eric Grossman, MD, Clinical Consultant / Clinipace Inc.
(b) (4)
Clara Li, MS, Regulatory Consultant / Clinipace Inc. (IND corresponding agent)
Maureen Merrifield, PhD, Regulatory Consultant / Clinipace Inc.
Cathy McCall, DPhil., Regulatory Consultant / Clinipace Inc.

1.0 BACKGROUND

On October 19, 2018 Provepharm SAS submitted a Type C meeting request to the Division of Medical Imaging Products.

As stated in the sponsor's meeting package, the sponsor has three main objectives for the meeting:

1. To obtain feedback from the FDA on the adequacy of the proposed overall data package to support a 505(b)(2) NDA application.
2. To obtain input from the FDA regarding the proposed indication.
3. To obtain FDA agreement that the clinical and non-clinical information package is adequate to support a future NDA submission for the proposed indication.

FDA sent Preliminary Comments to Provepharm SAS on January 14, 2019.

2.0 DISCUSSION

We have reviewed the meeting package submitted on October 19, 2018, and provide the following responses to your questions:

Clinical:

Question 1a: Provepharm believes it has a made good faith effort to identify and analyze all relevant literature available to support the safety and diagnostic accuracy and convenience bestowed by the contrast dye indigo carmine when used as a

visualization aid during cystoscopy. Does the Division agree?

FDA response to question 1a:
Yes, we agree that you have made a good faith effort to identify literature to support the drug when used as a visualization aid during cystoscopy. However, your proposed indications are much broader than use of indigo carmine during cystoscopy. If you wish to pursue a broad indication, you will need to expand your literature search for additional evidence of efficacy. Also, please see responses to questions 1c and 1d.

Meeting Discussion: The sponsor stated they have (b) (4) The sponsor requested clarification

Question 1b: Since no studies were identified that directly assess whether the use of indigo carmine produces an additive advantage to visualization by cystoscopy alone, we believe that a clinical study must be conducted to provide this required information. Provepharm therefore proposes to conduct a single clinical study for that purpose. A summary of the proposed study is included in this briefing document. Does the Division agree that the literature data are insufficient to show an additive advantage of the dye and a clinical study is required?

FDA response to question 1b:
Yes, we agree that a clinical study is needed.

Question 1c: Provepharm believes that, if positive, the proposed clinical study supplemented with the supportive (indirect) information obtained via the literature searches on the value of intraoperative cystoscopy would provide adequate data for the indication for indigo carmine as follows. Does the Division agree?

FDA response to question 1c:
We agree that supportive evidence for the safe and effective use of indigo carmine for determining ureteral patency can be obtained from literature.

Question 1d: To address physician satisfaction in the clinical protocol, Provepharm believes that the statemen (b) (4) is sufficient to demonstrate the clinical endpoint of indigo carmine in the proposed clinical study. Does the Division agree this evidence is sufficient to demonstrate that Indigo Carmine was (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures in visually (b) (4)

FDA response to question 1d:
We have reviewed your proposed clinical trial synopsis and have the following recommendations.
1) Visual analog scale to assess ureteral patency.

a) **Develop an ordinal scale to be used by the surgeon to determine whether there is no visualization, inadequate visualization, or adequate visualization of ureteral orifice outflow.**
b) **Prespecify criteria for classifying visualization as inadequate or adequate.**

Meeting Discussion: The sponsor agreed with a 3-point scale and will provide the categories in a formal written response. The scale will likely have the following categories: visualization, no visualization, and equivocal visualization. The FDA reiterated the scale is needed to minimize bias.

2) **Primary efficacy outcome.**
   a) **Evaluate the efficacy of indigo carmine (IC) for the assessment of ureteral patency, by comparing the pre-IC injection score (saline control) with the post-IC injection score in each of the two study arms. One comparison is for 2.5 mL IC and the other comparison is for 5 mL IC.**
   b) **Assess each ureteral orifice.**

3) **Independent, central, blinded assessment of ureteral patency.**
   a) **For each study patient capture the endoscopy images (after saline and after IC injection) used by the surgeon to assess ureteral patency.**
   b) **Pool all the saline images and all the IC images in two separate groups.**
   c) **Present the images following saline injection and the images post-IC injection in a randomized fashion to an independent blinded reader for scoring.**
   d) **Assess concordance between the surgeon and the blinded reader scores.**

4) **Statistical considerations.**
   a) **In addition to randomizing subjects to either 2.5 mL or 5 mL arm, we recommend that the surgeon who reads the images locally be blinded to the dose arm.**
   b) **Given two primary efficacy analyses will be performed (2.5 and 5 ml arms), please propose a multiplicity adjustment method (stepwise or single step).**
   c) **Please re-calculate the sample size required for the study to detect a hypothesized treatment effect based on the recommended primary endpoint based on an ordinal scale.**
   d) **Submit your Statistical Analysis Plan (SAP) for our review. The plan should be finalized prior to trial initiation.**

Meeting Discussion: The FDA and the sponsor agreed that the primary endpoint would be determined by the surgeon and by an independent reader. The primary analysis would be based on the surgical assessment. The FDA further stated that powering of the study should be based on patient level (both ureters to be examined) and sample size for the study will need to be recalculated based on the number of patients. The sponsor was encouraged to include preliminary estimated sample sizes along with the associated parameter assumptions at the time of submitting their meeting minutes.

5) **Patient follow up.**
We recommend that study patients be followed for 30 days (minimum of 1 week) to assess for unsuspected ureteral injuries or other complications.

Meeting discussion: The sponsor proposed (b) (4) up for assessment of surgical complications. The FDA recommended one month. The sponsor agreed with one month follow-up.

Question 1e: Provepharm believes that because of the lack of studies in the literature that directly assessed the additive advantage of indigo carmine (see Question 1b) any applicant for a 505(b)(2) NDA Indigo Carmine indication must first perform a clinical trial to verify the correct volume to be administered and to determine the pharmacokinetics and timing of the response. Does the Division agree?

FDA response to question 1e:
We believe the study, as proposed, will address the pharmacokinetics and timing of response. However, the proposed study will not support a visualization claim, as currently designed. Please refer to our response to 1d.

Question 2: *Since the necessary studies are impossible or highly impracticable (because, for example the number of patients is so small or the patients are geographically dispersed)* (per Section 505B(a)(4)(A)(i) of the Act), (b) (4)

FDA response to question 2:
No, we do not agree (b) (4) Indigo carmine has been used in pediatric procedures such as intraoperative assessment of vesicoureteral reflux and for evaluation of ureteral trauma. We recommend your iPSP address the potential benefit of indigo carmine for these pediatric uses, considering the potential to extrapolate efficacy from adult patients. The iPSP should include a rationale for extrapolation of efficacy from adults to pediatric patients and outline available information on pediatric dosing and pediatric safety concerns supported by published literature.

Meeting Discussion: The sponsor stated they will submit the iPSP within 60 days and will propose the use of indigo carmine plasma concentration data (AUC and C_{max}) to extrapolate efficacy from adult patients and use adult PK data to support dosing in the pediatric population. FDA agreed.

Clinical and Nonclinical

Question 3a: Does the Division agree that additional clinical pharmacology data regarding the parent compound and any major metabolites are required prior to submitting a 505(b)(2) application?

FDA response to question 3a:
Yes. Additional clinical pharmacology data regarding the parent compound and any major metabolites are required, if not already documented in the literature. If this data is not available in the literature, metabolite information can be acquired in your proposed PK study (Appendix 1).

Question 3b: Provepharm believes the proposed single clinical study (synopsis provided in Appendix 1) will be sufficient to address the FDA's human pharmacokinetics requirement for Provepharm indigo carmine. Does the Division agree?

FDA response to question 3b:
Yes, from a clinical pharmacology perspective, we agree.

Labeling

Question 4: In general, does the Agency agree that the information provided in the draft of the SPL provided by Provepharm for indigo carmine 40 mg/5 mL solution for injection, which is based mostly upon data from the literature, supplemented with PK and efficacy data obtained from the proposed clinical study provides sufficient information to create labeling for indigo carmine 40 mg/5 mL solution for injection as an approved US product?

FDA response to question 4:
The totality of the evidence you will provide to evaluate the safety and efficacy of your product for the proposed indication should be used to craft a label to inform the use of your product. The format of the annotated draft labeling text you provided on October 19, 2018, to detail the origin of the included information, appears adequate.

In addition to your annotated draft labeling, provide your label as word document that complies with the Physician Labeling Rule (PLR) format. We note, however, that your proposed annotated labeling does not conform to 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 See PRESCRIBING INFORMATION (below) for additional instructions, including a link to the *PLR Requirements for Prescribing Information* website which contains a sample PLR template.

Meeting Discussion: The sponsor asked if other companies planning to submit indigo carmine products will have the same standards applied to them. The FDA replied that discussions held with other sponsors cannot be shared but stated that the FDA is consistent with the advice given to all sponsors.

The FDA also stated that finalizing the indication of the drug will be determined after review of the submitted data.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful

pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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 the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

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 OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 PRESCRIBING INFORMATION

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

5.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

6.0 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.				

7.0 505(b)(2) REGULATORY PATHWAY

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

If you intend to submit a 505(b)(2) application that relies for approval 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.

8.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

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

9.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

10.0 ACTION ITEMS

None

11.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

ALBERTA E DAVIS WARREN
01/30/2019 12:41:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 137856

MEETING MINUTES

Provepharm SAS
Attention: Clara Li
Vice President, Regulatory and Strategic Development, Clinipace
US Agent to Provepharm SAS
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

Dear Ms. Li:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Indigo Carmine (Indigotindisulfonate Sodium Injection, USP).

We also refer to the teleconference between representatives of your firm and the FDA on February 20, 2018. The purpose of the meeting was to obtain feedback from the FDA on the adequacy of the proposed overall data package to support a 505(b)(2) NDA application; obtain input from the FDA regarding the proposed indication and to obtain FDA agreement that the non-clinical and clinical information in the literature is adequate to support a future NDA submission for the proposed indication.

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

If you have any questions, call meat (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Modupe Fagbami
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
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:	Pre-IND
Meeting Date and Time:	February 20, 2018 at 4:00 pm
Meeting Location:	Teleconference (WO, Building 22, Conf. Room 5440)
Application Number:	PIND 137856
Product Name:	Indigo Carmine (Indigotindisulfonate Sodium Injection, USP
Indication:	Intra-operative identification of ureteral orifices and other biological structures, during cystoscopy, abdominal and pelvic surgery, and ureteral catheterization.
Sponsor:	Provepharm SAS (Represented in the US by Clinipace, Inc.)
Meeting Chair:	Louis Marzella, M.D., Ph.D., Director, DMIP
Meeting Recorder:	Modupe Fagbami, Regulatory Project Manager, DMIP

FDA ATTENDEES

Louis Marzella, M.D., Ph.D., Director, DMIP
Alex Gorovets, M.D., Deputy Director, DMIP
Nushin Todd, M.D., Ph.D., Clinical Team Leader, DMIP
Michele Fedowitz, M.D., Associate Director, DMIP
Betsy Ballard, M.D., Medical Officer, DMIP
Ronald Honchel, Ph.D., Pharmacology/Toxicology Reviewer, DMIP
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCPV
Eldon Leutzinger, Ph.D., CMC Team Leader, OPQ/NDPBVI
Sue Jane Wang, Ph.D., Acting Deputy Division Director, OMPT/CDER/OTS/OB/DBI
Sungwon Lee, Ph.D., Statistics Reviewer, OMPT/CDER/OTS/OB/DBI
Carolyn Yancey, M.D., Pediatrics Reviewer, OMPT/CDER/OND/ODEIV/DPMH
Gettie Audain, Regulatory Project Manager, OMPT/CDER/OND/ODEIV/DPMH
Modupe Fagbami, Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

Mary Jane Helenek, Executive Vice President and Chief Operating Officer Provepharm Inc.
Marc Tokars, Vice President, Clinical Operations, Provepharm Inc.
Pablo Gluschankof, Ph.D., CDO, Deputy Director, Provepharm Inc.

Emilie Huyghues des Etages, Deputy R&D Director, and Head of Innovation, Provepharm SAS
Eric Grossman, M.D., Clinical Consultant, Clinipace Inc.
(b) (4)
(b) (4)
Clara Li, Regulatory Consultant, Clinipace. US Agent
Maureen Merrifield, Ph.D., Regulatory Consultant, Clinipace, Inc.
Stephanie Roland, B.Sc., Regulatory Consultant, Clinipace Inc.

BACKGROUND

The Sponsor, Provepharm SAS (Represented in the US by Clinipace, Inc) submitted this Type B meeting request on December 20, 2017, to: obtain feedback from the FDA on the adequacy of the proposed overall data package to support a 505(b)(2) NDA application; obtain input from the FDA regarding the proposed indication; and to obtain FDA agreement that the non-clinical and clinical information in the literature is adequate to support a future NDA submission for the proposed indication.

Indigo Carmine is indicated for use in the intra-operative identification of ureteral orifices and other biological structures during cystoscopy, abdominal and pelvic surgery, and ureteral catheterization.

FDA sent Preliminary Comments to Clinipace, Inc. on February 16, 2018.

DISCUSSION

1. Indigo carmine is a well-known molecule and Provepharm plans to produce a drug product that is equivalent in formulation to the currently marketed products in the US and EU (i.e. 40 mg/5 mL solution for injection: each mL contains: indigotindisulfonate sodium 8 mg, (b) (4) pH adjusted, when necessary, with citric acid and/or sodium citrate). Provepharm's indigo carmine product will meet USP specifications for Indigotindisulfonate sodium injection. Indigo carmine is a contrast stain which identifies tissues and structures by its deep blue color and is not metabolized for its intended mode of action. Therefore, it is expected that Provepharm's product will behave the same in the body as compared to the indigo carmine previously described in the literature.

   For the planned 505(b)(2) NDA submission Provepharm plans to rely on literature data to support the indication of: (b) (4) No additional clinical or nonclinical studies are planned.

   a. Does the Agency agree the literature data and USP conformance are adequate to support the writing of the Prescribing Information and the approval of a 505(b)(2) NDA in the proposed indication without a clinical study with the Provepharm product?

FDA Response:

We recommend that you develop a protocol for conducting a systematic review and analysis of the literature using publications containing data from adequate and well controlled clinical investigations. You will need to establish criteria for study quality based on factors such as prospective design, endpoints, and analysis plan, well defined truth/reference standard or comparator, minimum numbers of study patients, clinically well-defined patient population (including the pediatric population if applicable), demographic information, information on the imaging drug including dosage, route of administration, accounting for missing data, adequate study conduct including minimization of bias. Please also analyse information related to the limitations of use of your product and other factors that you identify.

When organizing your literature review, please categorize the data by clinical application. The literature to support the specific indication should be provided along with a discussion of how each article supports the specific indication(s) you have requested.

Meeting Discussion:

The Agency will consider a "good faith effort" approach and description of the process taken to reach the authors if documented in the NDA.

The Agency emphasized that such literature review should focus on the evidence that the dye is useful, but appreciates that it might be difficult to obtain information from a prospective, randomized study comparing post-surgery complications from using and not using indigo carmine. Conducting a study might be difficult and available publications may be limited.

The Agency will consider the totality of the data and other types of information. The Agency recommends that the Sponsor request another meeting for a more in-depth review and discussion of the available information and proposed submission.

b. Does the Agency agree that the literature data are adequate to support the proposed indication of: (b) (4)

FDA Response:

References should be to any clinical trials and/or animal studies necessary to the approval of each of the indications you are seeking (visualization of anatomic structures, (b) (4) etc.)

Meeting Discussion:

It was agreed that a structural (b) (4) ***ould be acceptable with a justification from the literature that*** (b) (4) ***Only study-based literature is supportive for the indication and label claims.*** (b) (4) ***Statements from those documents must be linked to the source publications.***

c. Does the Agency have any additional comments on the proposed indication?

FDA Response:

The labeled indication(s) should be drawn from the general categories for medical imaging products (i.e. delineation, disease of pathology detection, functional assessment, or diagnostic and therapeutic management).

Please refer to our guidance: ***Developing Medical Imaging Drug and Biological Products: Part 2: Clinical Indications.***
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071603.pdf

Meeting Discussion: There was no further discussion on this item at the meeting.

2. Per the FDA Guidance: How to Comply with the Pediatric Research and Equity Act, "*In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations.*" Since the most frequent use for indigo carmine is for intraoperative cystoscopy after urogynecological surgeries (e.g. hysterectomies, pelvic organ prolapse, and incontinence surgeries) which are typically conducted in adult populations, Provepharm believes that pediatric studies are not applicable for the proposed indication.

Since the necessary studies are impossible or highly impracticable (because, for example the number of patients is so small or the patients are geographically dispersed) (per Section 505B(a)(4)(A)(i) of the Act), Provepharm believes (b) (4) Does the Division agree?

FDA Response:

We disagree with (b) (4) (b) (4) **Clinical pediatric use of Indigo Carmine Injection includes intraoperative structural assessment of vesicoureteral reflux, ureteral trauma, and/or, in the case of a patient with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, an**

alternative in whom other intraoperative products (methylene blue) are contraindicated.

You will need to submit an initial Pediatric Study Plan (iPSP) that should provide use data on pediatric procedures performed intraoperatively with Indigo Carmine Injection or a similar intraoperative imaging agent. Your iPSP should include a plan for submitting a pediatric assessment based on published literature and/or clinical practice guidelines, or describe planned pediatric studies. If you propose to extrapolate use of Indigo Carmine Injection from adults to pediatric patients, you should provide your rationale for using extrapolation and provide epidemiology information to support any planned requests for waivers in any pediatric age group and planned request for a deferral of pediatric study.

Please be advised that under the FDA Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP-2) meeting. Refer to the draft guidance below.

Meeting Discussion:

(b) (4)

It was confirmed that this meeting is a pre-IND meeting and that the time clock for the iPSP will start after the EOP2 meeting.

NONCLINICAL QUESTION

3. Does the Division agree that the nonclinical literature data is adequate to support a 505(b)(2) NDA for the proposed indication and no additional nonclinical data would be required?

FDA Response:

Based on the information you provided in the meeting package, the nonclinical literature does not appear to be sufficient to support the proposed dose using the intravenous route of administration as per ICH M3(R2). However, the clinical safety experience with indigo carmine might provide the additional support needed. We do not recommend that additional nonclinical studies be performed at this time. You should include all relevant nonclinical manuscripts and data (particularly studies using the intravenous route of administration) in your NDA submission.

Meeting Discussion: There was no further discussion on this item at the meeting.

LABELING QUESTION

4. In general, does the Agency agree that [redacted (b) (4)]

FDA Response:

We appreciate the inclusion of the existing prescribing information as a reference and to inform the post-marketing experience for your product; however, [redacted (b) (4)] Your prescribing information will need to be based on the data and other information that is specific to your drug product and the pharmacologic class.
In addition, the format of your label will need to conform to the Physician Labeling Rule (PLR) format, which these examples do not. Please see additional advice under PRESCRIBING INFORMATION.

Meeting Discussion: There was no further discussion on this item at the meeting.

ADDITIONAL COMMENTS

Clinical Pharmacology:

1) **For each indication/population, the NDA include justification of the dose and timing of visualization being recommended in the package insert. The origin of the dose and timing are of interest – what was the basis for the selection of dose(s) and timing in early development? The need for justification of dose and timing extends to the pediatric population; size-based dosing and changes to timing should be discussed. The NDA should include any raw data available, the results of literature searches (and description of the search strategies), and discussion of the issues.**

2) **Our review will include an attempt to discern if intrinsic factors [e.g. renal impairment, hepatic impairment, disease, age (including changes across pediatric ages), sex, body weight] and extrinsic factors (e.g., concomitant drugs) alter effectiveness, safety, or pharmacokinetics. Accordingly, the NDA should include any raw data available, the results of literature searches (and description of the search strategies), and discussion of these issues.**

3) **The proposed package insert should include what is known regarding**
   A) **the identify of any major metabolites and the activities (safety-related) of such metabolites,**
   B) **how the parent drug and any major metabolites are eliminated and excreted,**
   C) **the ability of parent drug and any major metabolites to act as substrates or inhibitors of drug metabolizing enzymes and transporters, and**

D) single-dose pharmacokinetics of parent drug and any major metabolites

Meeting Discussion: There was no further discussion on this item at the meeting.

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.

DATA STANDARDS FOR STUDIES

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

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

This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

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).

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*

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were

approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.
The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

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

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

a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

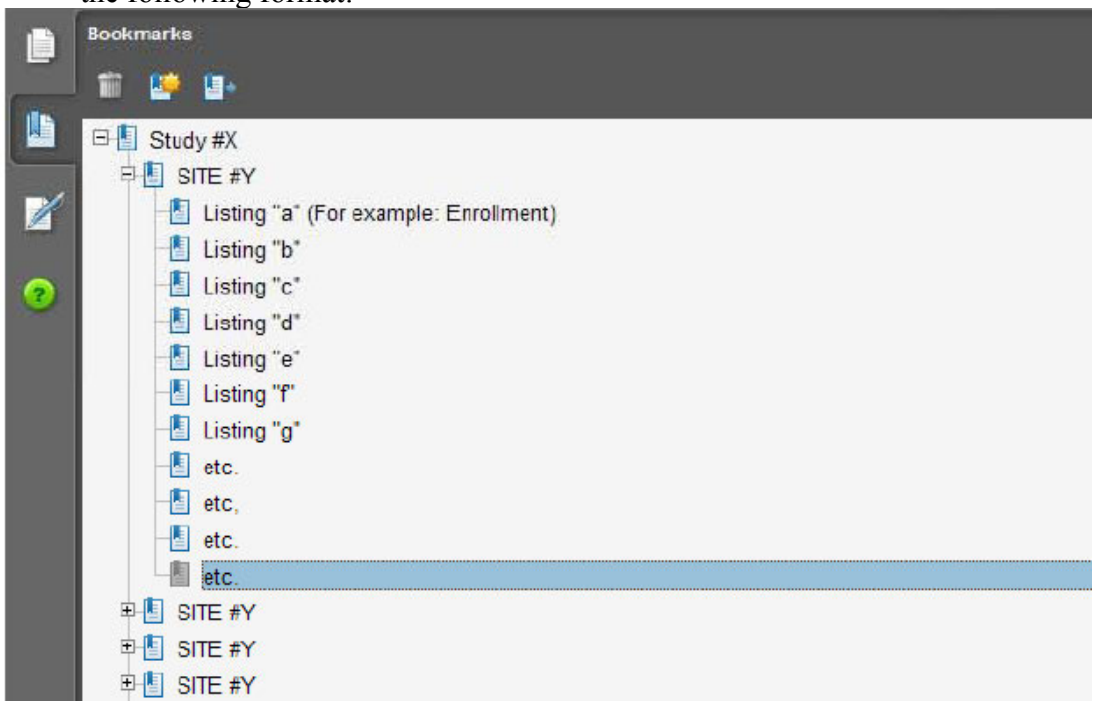
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

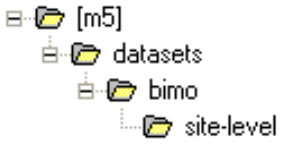
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide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

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

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

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

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



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

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

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

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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.

/s/

LIBERO L MARZELLA
03/20/2018