CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211580Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 135996

MEETING MINUTES

Novadaq Technologies Inc. (NOVADAQ)
Attention: Lori Swalm
Vice President Regulatory, Clinical and Economic Affairs
(US Representative for Novadaq Technologies Inc. (NOVADAQ))
9863 Elmcrest Drive
Dallas, Texas 75238

Dear Ms. Swalm:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Indocyanine Green (IC2000).

We also refer to the meeting between representatives of your firm and the FDA on November 14, 2017. The purpose of the meeting was to discuss formatting and regulatory issues with the Division of Medical Imaging Products (DMIP) to address any issue appropriately prior to the submission of the NDA.

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

If you have any questions, call me at (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-NDA
Meeting Date and Time:	November 14, 2017, at 12:30 pm
Meeting Location:	WO, Building 22, Conference Room 1421
Application Number:	PIND 135996
Product Name:	Indocyanine Green (IC2000)
Indication:	Lymphatic Mapping
Sponsor:	Novadaq Technologies Inc. (NOVADAQ)
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
Charles Ganley, M.D., Director, ODEIV
Nushin Todd, M.D., Ph.D., Clinical Team Leader, DMIP
Betsy Ballard, M.D., Medical Officer, DMIP
Jagjit Grewal, Associate Director, Regulatory Affairs, ODEIV
Jonathan Cohen, Ph.D., Pharmacology/Toxicology Reviewer, DMIP
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCPV
Sam Habet, Ph.D., Clinical Pharmacology Reviewer, DCPV
Eldon Leutzinger, Ph.D., CMC Team Leader, OPQ/NDPBVI
Sue Jane Wang, Ph.D., Acting Deputy Division Director, OMPT/CDER/OTS/OB/DBI
Jyoti Zalkikar, Ph.D., Secondary Statistical Reviewer, OMPT/CDER/OTS/OB/DBI
Anthony Mucci, Ph.D., Statistics Reviewer, OMPT/CDER/OTS/OB/DBI
Colin Kejing Chen, Ph.D., Biomedical Engineer, OMPT/CDRH/ODE/DSD/GSDB1
Neil Ogden, Ph.D., Supervisory Biologist, OMPT/CDRH/ODE/DSD/GSDB1
Maryam Mokhtarzadeh, M.D., Medical Officer OMPT/OSMP
Kristina Lauritsen, Ph.D. Product Jurisdiction Officer, OMPT/CDER/OEP
Modupe Fagbami, Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

Lori Swalm, Sr. V.P., Regulatory, Clinical and Economic Affairs, Stryker
Mike Hilldoerfer Sr. Director, Regulatory Affairs and Clinical Sciences, Stryker
Matt McKittrick, Director of Clinical Development, Stryker
Jen Pendlebury, Director of Regulatory Affairs, Stryker
Michael Frumovitz M.D., M.B.A., MD Anderson Cancer Center,
University of Texas, Houston, TX

BACKGROUND

Novadaq Technologies Inc. (NOVADAQ), Sponsor of PIND 135996 requested this Type B, Pre-NDA meeting on June 28, 2017. NOVADAQ will be filing an NDA as a 505(b)(2) for the approval of Indocyanine Green [(ICG) IC2000. The purpose of this meeting is to discuss formatting and regulatory issues with the Division of Medical Imaging Products (DMIP) to address any issue appropriately prior to the submission of the NDA.

FDA sent Preliminary Comments to Novadaq Technologies Inc. (NOVADAQ) on November 9, 2017.

QUESTION 1

We have provided information regarding the design, endpoints and preliminary results for the FILM study. This trial was reviewed by the CDRH under IDE G150254. It is our understanding that as a trial combining use of a drug (IC2000) and device (PINPOINT), review of the trial from a drug perspective was also conducted by DMIP/CDER. Is our understanding correct and, since the primary and secondary endpoints for the trial were reached, do the data meet the DMIP requirements to support the proposed lymphatics indication?

FDA RESPONSE:

We confirm that IDE G150254 was reviewed by CDRH and CDER and that both centers contributed to the Agency's advice. We encourage you to submit your application for our review. We will determine the adequacy of the data to support the proposed lymphatics indication after we complete the review of the data and other information in your application.

FDA Response:

Sponsor at this meeting purposely wanted to present the FILM study Primary and Secondary endpoints. Sponsor understood that the protocol was reviewed by both CDER and CDRH and that the results will be assessed by the Agency when the NDA is submitted. The Sponsor is targeting December 31, 2017, to submit the NDA.

QUESTION 2

We have provided information regarding the results from a meta-analysis of ICG for use in identification of lymph nodes in patients with cervical and uterine cancer. Together with the data from the FILM study, does the data meet the DMIP requirements to support the proposed lymphatics indication in a 505(b)(2) NDA?

FDA RESPONSE:

The study design for the FILM trial and the review of the literature can potentially support a lymphatic mapping claim (see our comments above). Additionally, we request that you include in your study report information on the histopathology (cancer status) of all excised nodes in the study patients.

FDA Response:

The Sponsor confirmed that the results from the systematic summary (meta-analysis) for lymphatic mapping in uterine and cervical cancer are consistent with the FILM trial and that histopathology data will be presented for meta-analysis from the FILM study.

The Agency enquired whether the existing angiography indications for SPY Systems, will be included in the application. The Sponsor confirmed that they would and that the data would be provided in the form of three separate meta-analyses (macro-vascular, micro-vascular and biliary anatomy). Within each meta-analysis, data would be separated by clinical application (i.e., coronary artery by-pass, large vessels in tissue transfer flaps etc.).

The Sponsor said that there will be published literature and the data from each protocol, being statistically analyzed, and as per prior discussions with the Agency, would only include studies with Novadaq devices.

In addition, the Sponsor said that there will be a summary of safety data and, as per prior discussions with the Agency, this would include data from published papers with ICG from different manufacturers.

The Sponsor said that the SLN node is determined and identified as secondary or lower echelon nodes by following the lymphatic vessels leading from the cervical injection site to the first node, which is the SLN, and then following vessels from this node to other nodes. This is possible with ICG, but the vessels cannot be seen with blue dyes and cannot be located with technetium-99.

The Agency added that since the NDA will include full manufacturing data an inspection of the ICG manufacturing facility and a full inclusive Module 3 will be required. The Sponsor acknowledged these requirements.

The Agency stated that the Sponsor will need to bridge their work from formulation(s) used in published studies to the proposed formulation which was used in the FILM study to provide justification for using studies from a different source of ICG.

(b) (4)

QUESTION 3

Does the design and endpoints of the angiography meta-analysis, assuming the endpoints are reached, meet the DMIP requirements under the 505(b)(2) submission pathway, to support the proposed angiography and visualization of extra-hepatic biliary ducts indications in a 505(b)(2) NDA?

FDA RESPONSE:
We have insufficient information to answer this question.

You plan to use a systematic review and analysis of published studies to support the angiography indications in your application. When organizing your literature reviews, please categorize the data by clinical application and device (e.g. lymph node mapping, lymphography).

We anticipate that your review would be guided by a protocol that describes in detail the criteria for study selection based on factors such as: prospective design and analysis plan, clinically meaningful endpoints, well defined 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, adequacy of study conduct including minimization of bias and accounting for missing data.

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

QUESTION 4
Novadaq will be filing an NDA under section 505(b)(2) for IC2000 for the indications described in section 4, above. The submission will be in electronic Common Technical Document (eCTD) format. Are there any other formatting issues that Novadaq should consider and address when preparing the NDA? We value any additional advice FDA may offer regarding our plans.

FDA RESPONSE:
Please submit all information submitted in standard format. The data sets should be in xpt.

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

ADDITIONAL COMMENTS:

- **Please clarify the source of nonclinical and clinical safety data (e.g., published literature) to support interstitial administration of Indocyanine Green for the proposed indication(s).**

- **If available, please provide** (b) (4)

- **You stated in your meeting package, p. 7, that the drug ICGreen is obtained from an approved source (NDA011525, ANDA 040811). Please confirm the ICGreen source and identify all proposed current manufacturing facilities.**

- **In the NDA, please summarize the dose(s) used in each study that contributes to the assessment of efficacy. For each study, include information on the dose selection. For each indication, summarize the information that indicates that the proposed dose is "near optimal." By "near optimal" we mean that lower doses are likely to be less**

efficacious and higher doses are likely to not be significantly more efficacious, unacceptable for safety, or both.

- **In the NDA, summarize available pharmacokinetics data regarding systemic absorption following interstitial injection.**

- **You propose to rely, in part, upon published literature to support your planned 505(b)(2) NDA. You must establish that reliance on the studies described in the literature is scientifically appropriate. Additionally, your application must include copies of the published literature articles that you intend to rely upon. Please see the "505(b)(2) Regulatory Pathway" section below for additional information.**

- **Your proposed drug product appears to be a pharmaceutical equivalent to NDA 011525 IC-Green 25 mg/vial. See the "505(b)(2) Regulatory Pathway" section below regarding the requirements if FDA has approved one or more pharmaceutically equivalent products prior to the submission of the 505(b)(2) NDA.**

Meeting Discussion: There was no meeting 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).

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

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

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

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

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an

appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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

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

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

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

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.

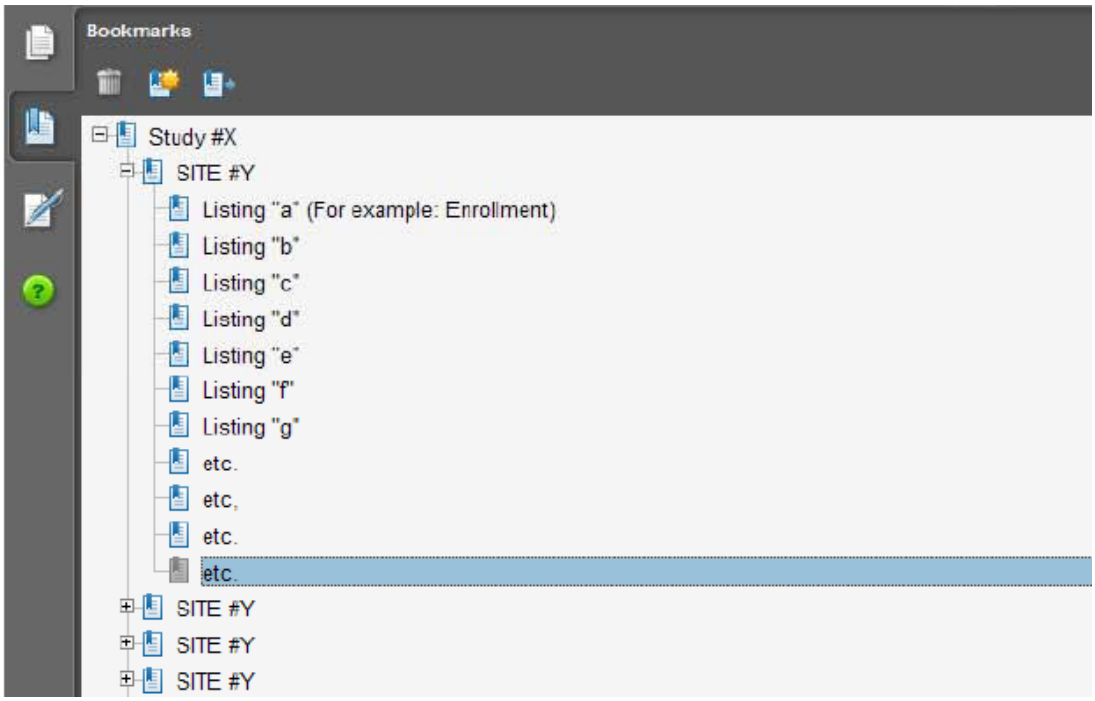
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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	STF File Tag	Used For	Allowable File Formats

Request Item[1]			
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

HANDOUTS
Below is the Sponsor's Presentation without the video.
The full Sponsor's presentation is in their official submission to the Agency of November 15, 2017.

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/s/

LIBERO L MARZELLA
12/06/2017