CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214517Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 214517
NDA 205677/S-007

REFUSAL TO FILE

Vanda Pharmaceuticals Inc.
Attention: Christos Polymeropoulos, MD
Medical Director
2200 Pennsylvania Avenue, NW, Suite 300-E
Washington, DC 20037

Dear Dr. Polymeropoulos:[1]

Please refer to your new drug application (NDA) dated and received January 13, 2020 (NDA 214517), and your supplemental New Drug Application (sNDA) dated and received January 21, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Hetlioz (tasimelteon) Suspension and Capsules, respectively.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Clinical Pharmacology

Both capsule and suspension formulations of tasimelteon were used in the double-blind efficacy and safety study (VP-VEC-162-2401). The Agency previously emphasized that it is important to demonstrate a pharmacokinetic (PK) bridge between capsule formulation and suspension formulation of tasimelteon in order to support the review of efficacy and safety results from Study VP-VEC-162-2401 (Please refer to Pre-sNDA meeting minutes for IND123408 dated December 11, 2019). Following submission of NDA 214517, we were unable to locate a relative bioavailability study comparing the PK of capsule and suspension formulations of tasimelteon. In response to our January 27, 2020, Information Request regarding the PK bridge, you provided the details of establishing a PK bridge between the capsule formulation and the suspension formulation using data from the adult PK study, Study VP-VEC-162-4101, and from the pediatric PK study, Study VP-VEC-162-4201. However, we do not accept cross-study comparison of data for the purpose of PK bridging between the to-be-marketed suspension formulation and the approved capsule formulation. There are several uncertainties recognized while comparing data from studies VP-VEC-162-4101 and VP-VEC-162-4201. These include: a) difference in patient populations in terms of age, gender, disease condition, and

[1] 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.

others; b) different formulations used in these studies; c) not a cross-over study; d) sparse PK samples collected in pediatric population may not adequately capture the Cmax of suspension formulation; e) the reported large variability in PK of tasimelteon adds further complication to the interpretation of the results. Therefore, to demonstrate the PK bridge between two formulations, a pivotal relative bioavailability study is required in healthy subjects under fasted conditions.

Microbiology

We acknowledge the Validation Report VA.400.361 – Microbial Limits and Antimicrobial Effectiveness Testing document (Section 3.2.P.5.3) provided in the original January 13, 2020 submission; however, summary data for Antimicrobial Effectiveness Testing (AET) of the drug product could not be located in the report. In addition, we acknowledge the following statement in the response to the January 31, 2020 Information Request (received February 14, 2020), "We reviewed the available AET validation reports for the pediatric suspension drug product and it is true that AET testing was only performed using a suspension batch containing the (b) (4) label concentration of (b) (4) …" However, the referenced AET validation reports could not be located in the application. Note that aqueous finished drug products labeled as multiple dose must meet the requirements of USP <51> AET or equivalent method to support the label claim. Therefore, provide summary data for AET of the drug product formulated with the minimum or less than the minimum (b) (4) concentration proposed in drug product release and/or stability specifications.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

Chemistry Manufacturing and Controls

In accordance with ICH Q1A(R2), we typically expect the NDA submission to contain at least twelve (12) months of long-term and six (6) months of accelerated stability data for three batches per packaging configuration of the drug product. You have provided stability data for only two primary stability batches ((b) (4) batches) per packaging configuration. In addition, these batches do not have 12 months of long-term stability data. While you have provided supportive stability data for batches manufactured by (b) (4), these batches have different fill-volume and/or container closure than those proposed for the commercial presentations. Therefore, provide 12 months of long-term and 6-months of accelerated stability data for at least three batches per packaging configuration. The data should include test for water loss for both the packaging configurations.

Biopharmaceutics

We were unable to locate the final dissolution method development report for the proposed tasimelteon oral suspension and in support of the proposed acceptance criterion. Include the final dissolution method development report and complete

dissolution profile data with your future resubmission. With the complete report, please include rationale and justification for the selection of the method/test conditions taking into consideration that, in general, paddle speed slower than 50 rpm would be more appropriate for the oral suspension.

Clinical Pharmacology
We were unable to locate the bioanalytical method validation report and bioanalytical report for tasimelteon and its metabolite for Study VP-VEC-162-4201. Please submit this information.

Clinical
With reference to our previous correspondence and the meeting minutes from the Pre-sNDA meeting held on November 13, 2019:

- Describe exactly how the primary endpoint was assessed and calculated
- Describe any additional work you have done to support the clinical meaningfulness of the observed change
- Provide support for the use of caregiver diaries, including the rater training offered to caregivers and information on the validity of second-hand reporting of sleep data in this population
- Provide a narrative of treatment sequence for each patient
- Provide data presentations showing each subject's scores on a given measure or subscale (or actigraphy recordings) longitudinally over time, with clear designation of corresponding treatment (e.g., washout, OL tasimelteon, placebo, etc.), and include the complete data sets from which they were derived.

In addition, a summary of post-marketing data and a debarment certification are missing in your submission package. You should provide this summary and certification when you resubmit your application.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application

and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, call Hiren Patel, Regulatory Project Manager, at 301-796-2087.

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

TIFFANY R FARCHIONE
03/12/2020 02:15:08 PM

IND 123408

MEETING MINUTES

Vanda Pharmaceuticals, Inc.
Attention: Christos Polymeropoulos, MD
Medical Director
2200 Pennsylvania Ave NW, Suite 300E
Washington DC, 20037

Dear Dr. Polymeropoulos, MD:

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

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2019. The purpose of the meeting was to discuss your development plan for the treatment of sleep disorder in Smith-Magenis Syndrome (SMS).

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sNDA

Meeting Date and Time: November 13, 2019 from 1:00 pm to 2:00 pm
Meeting Location: White Oak, Bldg 22, Room 1417

Application Number: IND 123408
Product Name: HETLIOZ (tasimelteon)
Indication: Smith-Magenis Syndrome (SMS)
Sponsor Name: Vanda Pharmaceuticals, Inc.

FDA ATTENDEES

Tiffany R. Farchione, MD	Director (Acting), Division of Psychiatry (DP)
Javier A. Muñiz, MD	Associate Director for Therapeutic Review, DP
Michael Davis, MD	Clinical Team Leader, DP
Yaseen Zimri, MD	Clinical Team Reviewer, DP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DP
Luning Zhuang, PhD	Clinical Pharmacology Team Leader, OCP
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Statistics Team Leader, Division of Biometrics I (DBI)
Eiji Ishida, MS	Statistics Reviewer, DBI
David Claffey, PhD	Product Quality Team Leader, OMPT
Gurpreet Gill-Sangha, PhD	Quality Assessment Lead, OLDP
Lin Qi, PhD	Product Quality Reviewer, OMPT
Lucas Kempf, MD	Rare Disease Medical Officer
Bill Bender, RPh	Senior Regulatory Project Manager

SPONSOR ATTENDEES

Mihael Polymeropoulos, MD	Chief Executive Officer
Christos Polymeropoulos, MD	Medical Director
Gunther Birznieks, MS-SVP	Business Development
Derek Xiao, PhD	VP, Head of Biometrics
Lauren Van Draanen	Corporate Strategy
Justin Brooks MD, PhD	Clinical
Maggie Miller	PRISMS
Charles Czeisler, MD, PhD	
Tim Williams	General Counsel

(b) (4)

1.0 BACKGROUND

Tasimelteon is a melatonin receptor agonist that was approved on January 31, 2014, as Hetlioz, for the treatment of non-24-hour sleep-wake disorder (non-24) under NDA 205677. Under IND 123408, the Sponsor, Vanda Pharmaceuticals, is currently developing tasimelteon for the treatment of the sleep disorder in Smith-Magenis syndrome (SMS), a rare genetic disorder that results in pervasive developmental delays and circadian rhythm disruptions. Tasimelteon was granted orphan-drug designation for the treatment of sleep-wake disorder in SMS by the FDA on April 30, 2010.

The Sponsor has conducted one clinical trial to evaluate the efficacy of tasimelteon for insomnia in SMS. This trial, VP-VEC-162-2401, consisted of two phases. In the first phase (referred to as 2401A), 11 patients (age 16 to 65 years), were treated with open-label tasimelteon 20 mg nightly for 9 weeks. The second phase (referred to as 2401B) had a double-blind, two-period, crossover design, in which 26 patients were randomized to receive tasimelteon 20 mg nightly then placebo (n=13), or placebo then tasimelteon 20 mg nightly (n=13) for 4 weeks each, separated by a 1-week washout period. Patients from 2401A and 2401B could enter an open-label extension phase consisting of 232 weeks of treatment.

Following submission of Amendment 9 to the study protocol received on 12/18/18, the Division sent an information request (IR) to the Sponsor on 12/28/18 that included a request for clarification of their change to the study endpoint.

- Prior to Amendment 9, the primary efficacy endpoint was “improvement in nighttime sleep defined as the reduction of the percentage of wake periods within the sleep interval.”

- With Amendment 9, the endpoint was changed to “improvement in nighttime sleep”.

Following further requests for clarification, the Sponsor indicated that “improvement in nighttime sleep” comprised two primary endpoints:

- Average of nighttime sleep quality (single-item caregiver rating) on the worst 50% of daily caregiver diary entries in the treatment period, and

- Average of subjective total nighttime sleep time on the worst 50% of daily caregiver diary entries in the treatment period.

The Sponsor has requested this Type B pre-sNDA meeting to discuss a supplemental New Drug Application (sNDA) for tasimelteon for the treatment of the sleep disorder in SMS associated with diurnal melatonin secretion. This meeting will be the first with the Sponsor for this IND.

The Sponsor's stated purpose for this meeting is to discuss the current dataset that they plan to file to support sNDA filing of tasimelteon for the treatment of the sleep disorder in Smith-Magenis syndrome (SMS).

2.0 DISCUSSION

2.1. General Category

Question 1: Does the Division agree that data from the pivotal efficacy study, VP-VEC-162-2401, including both the open-label phase as well as the double-blind randomized cross-over phase of the study are adequate to inform labeling for an indication of the treatment of the sleep disorder in Smith Magenis Syndrome?

FDA Response to Question 1: *Whether the described trials are adequate to assess efficacy and inform labeling for the proper use of this drug in this population will be a matter of review under the NDA. As noted in the draft Guidance for Industry: Rare Diseases: Common Issues in Drug Development, the standard of evidence required to establish efficacy "is the same for all drugs regardless of whether they are for common or rare diseases." The trials as designed and described are difficult to interpret. For example, you have not provided clear evidence to support the validity of the primary endpoints in this population or the clinical meaningfulness of the effects observed for either of your primary outcome measures in the study in this population.*

We note that there has not been an agreement on the choice of the primary efficacy evaluation (endpoint and analysis) between you and the FDA. We recommend that in addition to your primary analysis, you construct exploratory analyses using all available efficacy data to support your efficacy claim. For instance, it may be informative (and, given the sample size, not unreasonable) to see changes over time plotted with each individual's change as a separate line to allow exploration of potential outliers. As another example, if you believe that improvements in sleep are related to downstream effects on behavior or other symptoms, you may wish to include additional analyses exploring that relationship to help support an evaluation of clinical meaningfulness.

In your NDA submission, it would be helpful if you can describe exactly how the primary endpoint was assessed and calculated. Any additional work you have done to support the clinical meaningfulness of the observed change should also be described in detail. You should provide support for use of caregiver diaries, particularly any data you have (in this population or others) to support the validity of second-hand reporting of sleep data. Please also include a description with supportive literature of the natural history of SMS.

> ***Discussion:*** *The Sponsor reported on their findings regarding characterization of sleep disturbance in an observational study of SMS patients receiving standard of care. The Division indicated that the complete report and all data from the*

observational study, including the nature and timing of treatments for insomnia and other concomitant therapies, should be included as supporting material in their sNDA submission.

The Sponsor reported on their open-label (OL) study and clarified that five subjects from the OL study entered a washout phase and were randomized in the double-blind (DB) cross-over study. The Sponsor clarified that they considered the OL study as suggestive of efficacy, providing support to the DB study which would be considered the registration study. The Division indicated that this was acceptable.

The Sponsor stated that they would provide a narrative of treatment sequence for each patient. The Division indicated that this would be important to facilitate sNDA review. The Division further requested that the submission include data presentations showing each subject's scores on a given measure or subscale (or actigraphy recordings) longitudinally over time, with clear designation of corresponding treatment (e.g., washout, OL tasimelteon, placebo, etc.) and include also the complete data sets from which they were derived. The Sponsor agreed.

The Sponsor reported on their DB study and explained their choice of endpoints. The Division sought clarification on additional details of the study. The Sponsor reported that the one-week washout period between treatments in the cross-over may have been shorter than desirable but was needed to ensure patients/caregivers would be willing to comply with the no-treatment period. The Division inquired if placebo or no drug was given during washout. The Sponsor reported no drug was given during washout. The Division also inquired whether the Aberrant Behavior Checklist was administered in the DB study. The Sponsor confirmed that it was.

The Sponsor further noted that in the DB study both capsule and liquid formulations of the oral study drug were used and sought confirmation of the acceptability of this approach. The Division indicated that if the Sponsor demonstrated a PK bridge between formulations this would be acceptable, and the adequacy of the supporting study and manufacturing procedures would be a matter of review. The Sponsor indicated they would submit their PK bridging study as part of the application.

The Sponsor indicated that they could provide genetic data for their study subjects. The Division indicated that such data should be provided using the International System for Human Cytogenetic Nomenclature, and the Sponsor confirmed that it would be.

Finally, the Sponsor noted that they planned to file by the end of the year (b) (4) *Details of the Sponsor's presentation are in the Sponsor slide-set appended to these meeting minutes.*

Post-meeting Comment: *We note that, although data from studies using the liquid formulation may be used to support the proposed efficacy supplement, we cannot*

approve a new dosage form under the current NDA. If you wish to market the liquid dosage form, you must submit a new original NDA for that dosage form. Provide the necessary CMC information for the liquid dosage form in this supplemental application to support the lots used in the clinical trial.

Question 2: Does the Division agree that the existing safety database described in NDA205677 2.5 Clinical Overview in combination with the safety data collected in the Smith-Magenis Syndrome indication described in Section 8 are adequate to inform labeling for an indication of the treatment of the sleep disorder in Smith-Magenis Syndrome?

FDA Response to Question 2: *In addition to the safety database supporting the approval of NDA 205677, you have open-label safety data from 19 patients and placebo-controlled safety data for 25 patients with SMS treated with tasimelteon from Study VP-VEC-162-2401, and additional uncontrolled safety data from the single-dose pediatric PK Study VP-VEC-162-4201 in blind children with non-24 and children with sleep disturbance and a neurodevelopmental disorder. On face, these safety data are sufficient for filing, based on the rarity of SMS, but their adequacy will be a matter of review should an sNDA be submitted.*

Discussion: *No further discussion.*

Post-meeting Comments

A description of the training and the training material for the caregiver completing the diary will be helpful to understand the interpretation of the scoring, because the standard free response field was not included in the scale.

All concomitant medications and therapies and changes in them should be documented at all phases of the studies.

When submitting genetic/genomic information to the Agency, the data should reflect both the intended clinical and regulatory use, as well as provide the testing methodology utilized. Because SMS is typically caused by a chromosomal deletion, the International System for Human Cytogenetic Nomenclature (ISCN) should be the standard utilized to report the identified genetic/genomic variant. If other genetic etiologies (that are not easily reported in this standard) are important to the interpretation and review of the sNDA, other standard nomenclatures may be appropriate, such as the Human Genome Variation Society (HGVS) Recommendations for the Description of Sequence Variants (http://varnomen.hgvs.org/). All identified variants (cytogenomic or sequence variants) should also be interpreted for clinical relevance. Interpretation of identified sequence variants should follow the standards and guidelines for sequence variant interpretation published jointly by ACMG and AMP

(https://www.acmg.net/docs/Standards_Guidelines_for_the_Interpretation_of_Sequence_Variants.pdf).

3.0 OTHER

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

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

- 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*.

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.[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

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

standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[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.

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

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

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[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.

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[4] https://www.fda.gov/media/88173/download
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[10]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[11]

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.

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[7] https://www.fda.gov/media/88173/download
[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[10] http://www.fda.gov/ectd
[11] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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)				

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*.[12]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items requiring further discussion.

6.0 ATTACHMENTS AND HANDOUTS

Please see Sponsor's slides.

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

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

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

/s/

TIFFANY R FARCHIONE
12/11/2019 10:31:05 PM