

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213801Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 069416

MEETING PRELIMINARY COMMENTS

Astellas Pharma Global Development, Inc.
Attention: Kristine Skjolaas, Ph.D.
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Skjolaas:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for YM178 (mirabegron) tablets and oral suspension.

We also refer to your August 15, 2019, correspondence, received August 15, 2019, requesting a meeting to discuss your planned new drug application, specifically, the overall clinical development program, the pediatric data package to fulfill PREA requirements as well as the terms of the Written Request, and your submission plans for the pediatric and adult populations.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to me, 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.

¹We 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>.

If you have any questions, please call me at 301-796-0875.

Sincerely,

{See appended electronic signature page}

Nenita Crisostomo
Regulatory Health Project Manager
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
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: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 14, 2019, at 1:00 PM – 2:00 PM, Eastern
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 069416
Product Name: YM178 (mirabegron) tablets and oral suspension

Indication: Treatment of neurogenic detrusor overactivity in pediatric patients

Sponsor Name: Astellas Pharma Global Development, Inc.

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 November 14, 2019, at 1:00 PM – 2:00 PM, in 10903 New Hampshire Avenue, Silver Spring, Maryland 20903 between Astellas Pharma Global Development, Inc. and the Division of Bone, Reproductive and Urologic 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. 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). Contact me, the Regulatory Project Manager (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

Myrbetriq (mirabegron), 25mg and 50mg tablets, were approved for marketing in June 2012 for treatment of overactive bladder (OAB) in adults. As required under the Pediatric Research Equity Act (PREA), postmarketing studies were conducted for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years

to < 18 years of age. Also, a Written Request (WR) for pediatric studies was issued on March 18, 2016.

Astellas has developed mirabegron extended-release granules which, when reconstituted in water, result in an oral suspension of 8 mg/mL. The suspension is intended for administration to pediatric patients with NDO below a specified cutoff weight and to patients above that cutoff weight who cannot swallow tablets.

Astellas requested this meeting to discuss the 1) pediatric package intended to fulfill PREA and WR, 2) submission plans for sNDA 202611 for mirabegron tablets and NDA 213801 for mirabegron granules for oral suspension for the treatment of pediatric NDO patients, and 3) (b) (4)

The Meeting Information Package was received on September 24, 2019.

2.0 DISCUSSION

2.1. Regulatory

Question 1 (Phase 3 Study 178-CL-206A): Does the Agency agree that the pediatric clinical development program as already conducted for mirabegron is sufficient to support the submission of an efficacy and safety supplement and new NDA for the proposed indication for mirabegron tablets and granules for treatment of NDO in pediatric patients aged 3 to < 18 years?

FDA Response:

A determination as to whether your program is sufficient to support the filing of a supplemental NDA and a new NDA for mirabegron tablets and granules for oral suspension, respectively, for the treatment of NDO in pediatric patients cannot be made prior to our preliminary review of the submissions. However, in general, your development program appears reasonable.

Question 2 (Compliance with Written Request): Does the Agency agree that the pediatric clinical development program as already conducted for mirabegron is consistent with the requirements under PREA and is sufficient to support a Request for Pediatric Exclusivity for mirabegron?

FDA Response:

A determination as to whether your pediatric clinical development program meets the PREA requirements and the terms of the WR cannot be made prior to our review of the submissions and presentation of the data before FDA's Pediatric Exclusivity Board. However, your pediatric development program appears to be sufficient to provide information to determine whether the PREA and Written Request requirements have been met.

Question 3

(b) (4)

FDA Response:

(b) (4)

2.2. Clinical

Question 4 (Integrated Summary of Efficacy): Does the Agency agree with Astellas' request to present the efficacy data as described above but not to provide an Integrated Summary of Efficacy?

FDA Response:

Yes.

Question 5 (Integrated Summary of Safety): Does the Agency agree with Astellas' proposed presentation of the safety analyses for use of mirabegron in the treatment of NDO in pediatric patients?

FDA Response:

Yes. In addition, we have the following requests for safety information in your NDA submission:

1. Submit case report forms (CRFs) and case narratives for all deaths, SAEs, and discontinuations due to AEs.
2. Provide a summary table, including all deaths, SAEs, and discontinuations due to AEs, categorized by system organ class (SOC) and preferred term (PT), with hyperlinks to the case narratives.

3. Provide case narratives for all 5 reported hypersensitivity AEs and for both reported cardiovascular AEs (mild QT prolongation and mild bradycardia).
4. Provide a detailed analysis of shifts from normal to abnormal vital signs, including categorical shifts upward in blood pressure and in heart rate, based on age-related normative reference values.
5. Given the open label nature of the study 178-CL-206A, provide the individual patient-level blood pressure and heart rate data along with information on potentially confounding factors that have been previously communicated to you. These factors include, but are not limited to, the timing of vital sign measurements relative to other study visit interventions (e.g., phlebotomy) and the patient demeanor during vital sign measurements. This information will assist in the clinical interpretation of changes from baseline in blood pressure and heart rate category.

Question 6 (Clinical Datasets): Does the Agency agree with the proposed plan for submission of electronic datasets in the planned sNDA to NDA 202611 and the new NDA 213801 for mirabegron?

FDA Response:

Yes, we agree with your proposed plan. In addition, submit the analysis programs.

Question 7 (Dosing and Administration): Does the Agency agree with the model-based approach for the development of the dosing recommendations for mirabegron (extended-release tablets and granules for oral suspension) in the pediatric population?

FDA Response:

Your model-based approach for dosing selection and recommendation appears generally acceptable. In your planned sNDA and NDA submissions, update your population PK modeling and simulations with all available pediatric data, including data from dosing with tablets and granules for oral suspension, to support the recommended dosing regimen in labeling.

Question 8 (Proposed Labeling Format)

Question 8a: Does the Agency agree with the proposal of a single mirabegron label inclusive of both the tablet and granules for oral suspension formulations and both the adult OAB and pediatric NDO indications?

FDA Response:

A single label covering multiple formulations may be acceptable. However, a detailed discussion of labeling, including whether a single mirabegron label inclusive of both tablet and granule for oral suspension formulations, is premature at this time.

We have the following additional comments:

1. We do not agree with your proposal to [REDACTED] (b) (4).
See our response to Question 3.
2. [REDACTED] (b) (4)
3. It appears that the new granules for oral suspension formulation may not be bioequivalent to the currently marketed tablet formulation and thus, not interchangeable on a mg to mg or 1:1 conversion basis. If both formulations are approved under a single label, specific information may be needed in labeling to reduce the risk of over- or under-dose medication errors.

Question 8b: Does the Agency agree with the proposed patient “Instructions for Use” for oral suspension in the “Pediatric Patient Information”?

FDA Response:

A detailed discussion of labeling, including the proposed “Instructions for Use” in the proposed PPI, is premature. The acceptability of the patient labeling will be a review issue.

Question 8c: Does the Agency agree with the proposed pharmacist instructions for reconstitution of the granules and supply of appropriate dosing device in the [REDACTED] (b) (4) subsection of the full “Prescribing Information”?

FDA Response:

A detailed discussion of labeling, including the proposed “[REDACTED] (b) (4)” in the proposed PI, is premature. The acceptability of the labeling will be a review issue.

Question 9 (Submission Content)

Question 9a: Does the Agency agree with the proposed submission plan of the sNDA to NDA 202611 mirabegron tablets?

FDA Response:

Yes.

We have the following technical comments:

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Silver Spring, MD 20993
www.fda.gov

1. Follow the CTD heading and hierarchy guidance at <https://www.fda.gov/media/76444/download> to place each document in the proper eCTD sub heading.
2. Because your application is in eCTD format, cross referencing has to be done in the leaf level of the xml backbone.
3. To use cross application link, both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. xlink:href=" ../ ../indXXXXXX/0009/m2/24-nonclinical-over/nonclinical-overview.pdf"). In the leaf titles of the documents, it is recommended that the leaf title indicate the words "cross reference to" and the application number (e.g. Cross Ref to indXXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.
4. Prior to using cross application linking in an application and to ensure successful use of cross application links, it is recommended that you submit an "eCTD cross application links" sample. However, if you have used cross application linking prior, there is no need for a cross application sample.
5. To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionsRequirements/ElectronicSubmissions/UCM315023.pdf>

Question 9b: Does the Agency agree with the proposed submission plan of the new NDA 213801 for mirabegron granules for oral suspension?

FDA Response:

Yes. However, Pharmacology written and tabulated summaries should be included in Module 2.6.

In addition, we remind you to follow the CTD heading and hierarchy guidance at <https://www.fda.gov/media/76444/download> to place each document in the proper eCTD sub heading.

Question 9c: Regarding PREA and pediatric exclusivity requirements for submission of associated reports to the original NDA 202611(tablets), does the Agency agree that the CSRs can be incorporated into NDA 202611 by a cross-reference to the new NDA 213801 (granules) and that this is acceptable for FDA review of pediatric exclusivity?

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FDA Response:

Yes.

2.3. Chemistry, Manufacturing and Controls

Question 10 (Drug Substance): Does the Agency agree with the proposal to cross-reference to Myrbetriq NDA 202611 for drug substance information for mirabegron in the planned new NDA 213801 for mirabegron granules for oral suspension?

FDA Response:

Yes, drug substance information may be incorporated into the NDA by cross-reference to NDA 202611. However, the new NDA should include complete drug substance manufacturing site information in 3.2.S.2.1 and in the Form 356h. Identify any pending drug substance-related supplements to NDA 202611 when the new NDA is submitted.

Question 11 (Stability Data in the NDA Submission): Does the Agency agree with the proposal to submit 9-month long-term primary stability data at the time of filing with 12-month long-term stability data and the corresponding in-use reconstitution data provided 30 days after the initial submission?

FDA Response:

Yes, we agree with the proposal to submit 9-months long-term stability data, along with 6-months accelerated stability data, for three registration batches at the time of initial submission, with 12-month long-term data and in-use stability data for the reconstituted product within 30 days of the initial submission. We note that the registration stability batches were manufactured in October and November 2018. If submission of the new NDA is delayed until 2020, we request that the 12-month data and the in-use stability data be submitted in the initial submission.

To ensure the adequacy of the drug product stability protocol and the reconstituted suspension in-use stability protocol, we recommend that you submit these protocols to the IND.

Question 12 (Prior Approval Inspection): Does the Agency agree with the proposal that the (b) (4) process validation is not required before the Prior Approval Inspection?

FDA Response:

Process Performance Qualification (PPQ) batch production, as discussed in FDA Guidance for Industry - Process Validation: General Principles and Practices, January 2011, is not required to be completed prior to a pre-approval inspection. However, PPQ must be successfully completed prior to commercial launch. We recommend that PPQ

production is carried out based on the FDA-approved manufacturing process and control strategies.

If the (b) (4) is critical to product stability (i.e., is 'functional'), the initial NDA submission should include data demonstrating the adequacy of the (b) (4) process at APEBV Meppel (e.g., 3 months accelerated stability data on three batches). Full validation (b) (4) of the (b) (4) process should be performed as described in the process validation guidance.

If stability data demonstrate that the (b) (4) have no impact on protection of the drug product, the PPQ for (b) (4) process can be waived as long as the equipment for (b) (4) process is qualified and demonstrated suitable for its intended purpose.

ADDITIONAL COMMENTS

Chemistry, Manufacturing and Controls (CMC)

Product Quality

1. Include a test for suspendability of the granules and a test for pH of the oral suspension when it is reconstituted as directed in the labeling to the drug product specification.

Biopharmaceutics

Dissolution Data Presentation:

In the dissolution method development report, and/or batch analysis section, present detailed experimental dissolution data as follows:

1. In the narrative portion of the dissolution report, include individual vessel data, in particular, investigation of selected equipment, media, agitation speed, etc.
2. In addition to the mean dissolution data presented in graphical and tabular formats, submit in the "Batch Analysis" section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel ".xls or .xlsx" format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.
3. Provide the dissolution data as described in the example below.

Example - Reporting of individual vessel dissolution data

Cell A1 – Identifying Batch/Lot Label, and dissolution method/media used

Cell A2 – blank

Individual Unit Number (starting from cell A3 numerical values signifying the test unit)

Use one sheet for each unique batch/lot. Label accordingly in Cell A1

	A	B	C	D	E	F	G	H	I	J
1	Test lot 12345 (QC method/QC media)									
2		1	2	4	6	8	10	12		
3	1	3	15	62	98	99	99	98		
4	2	3	15	64	94	92	95	95		
5	3	3	9	37	80	96	97	97		
6	4	4	13	44	79	97	98	99		
7	5	3	12	39	71	96	98	98		
8	6	3	14	60	98	97	99	99		
9	7	4	13	44	82	93	98	98		
10	8	5	22	89	97	98	97	97		
11	9	4	16	64	96	98	96	96		
12	10	4	14	57	98	96	99	99		
13	11	4	16	63	96	96	97	97		
14	12	6	22	87	96	93	96	96		
15										
16										
17										
18										
19										
20										
21										
22										

Sampling Times (starting from cell B2 numerical values indicating collection times (minutes or hours))

Dissolution Data (starting from cell B3 numerical values indicating percent drug release)

Sheet1 Sheet2 Sheet3

- Follow the instructions provided in “**Specifications for File Format Types Using eCTD Specifications**” – updated March 2, 2017 (link below).

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionsRequirements/ElectronicSubmissions/UCM347471.pdf>.

Dissolution Acceptance Criterion:

For the selection of the dissolution acceptance criterion of the proposed drug product, consider the following:

- Use the multi-point dissolution data (n=12, sampling every 2 hours) from the pivotal clinical/PK drug product-batches and primary registration batches for the setting of the dissolution acceptance criterion of the proposed drug product (i.e., sampling time points and limits) to cover the beginning, intermediate and later stages of the dissolution profile. The recommended range at any dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. When applicable, include the dissolution profile data to support in-process dissolution acceptance criteria. Select the last sampling time point where $Q = \frac{(b)}{(4)}$ % dissolution occurs.
- Ensure that the in vitro dissolution profile is complete and that the plateau of drug dissolved is reached (i.e., no increase over 3 consecutive time-points).

3. Base the dissolution acceptance criterion on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12).
4. Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the eCTD.

Dissolution Acceptance Criterion/Criteria Recommendation:

We remind you that our recommendation on the adequacy of the proposed dissolution acceptance criterion/criteria for the proposed drug product will be made during the review based on the totality of the provided dissolution data.

IN SILICO PBPK MODELING SUPPORTING DS and/or DP ATTRIBUTES

To aid in the regulatory-decision making in terms of setting the appropriate acceptance criterion(a) for drug substance (DS) or drug product (DP) attributes (e.g., drug substance particle size, drug product hardness, drug product dissolution) based on in silico physiologically-based pharmacokinetics (PBPK) modeling, provide the following information/data (if available):

1. Relevant *in vivo* data (e.g., BA/BE, PK data) to demonstrate that drug product-batches with your proposed acceptance criterion(a) for drug substance or drug product attributes have a similar systemic exposure compared to that of the pivotal bio-study drug product-batch.
2. Available supportive data from *in silico* physiologically-based pharmacokinetics (PBPK) modeling and simulation demonstrating the *in vivo* impact at the extremes of the proposed drug substance and/or drug product attributes. For this purpose, submit the following information:
 - a. A modeling summary report, that provides an overview of the modeling strategy and details the modeling procedures, including model development, verification/validation, and application in a step-wise manner. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.
 - b. Detailed information on the inputs used in the development, optimization and verification/validation of the model(s). All physiological and physicochemical parameters, as well as their sources should be clearly specified. While we acknowledge that some input parameters are estimated (optimized), when the parameters are optimized, the initial value selection, the estimation method, the justification for the optimization algorithm, and the assumption(s) used should be provided. For simulation, provide the input values/ranges of

- parameters, single or population simulation (number of simulated subjects) and the output report.
- c. The definition file(s) listing all input and output files, and the use or purpose of each of these files, in an appropriate format (e.g., .pdf, .xpt,.xls).
 - d. Although we do not request the use of a specific software, due to substantive differences in software/versions, clear identification of software parameters is critical, which should include: name and version of the software, and (for custom modeling software) schematics of model structure and differential equations.
 - e. The methodological approach for model verification/validation, results verification/validation, and sensitivity analyses to interrogate the robustness of the model should be clearly presented. We expect that PK data may contribute to establish confidence in model appropriateness when addressing the study question(s).
 - f. The generated data from the verified/validated model to address the study question(s) should be presented using tables, figures and text where appropriate.
 - g. The complete PBPK modeling and simulation report, definition files, and datasets in module 5.3.1.3 of the eCTD.
3. Our final decision regarding the acceptability of the acceptance criterion(a) of the drug substance and/or drug product attributes will be made during the review of your submission based on the totality of the supportive data and relevant information, including quality demonstration of submitted PBPK modeling and simulation work.

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.

We acknowledge your agreed Initial Pediatric Study Plan (iPSP) dated December 11, 2013.

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 Information² and Pregnancy and Lactation Labeling Final Rule³ 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,

² <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

³ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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.

5.0 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)				

6.0 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*.⁴

⁴ <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/

NENITA I CRISOSTOMO
11/06/2019 12:40:35 AM