CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216185Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 140785

MEETING REQUEST-
WRITTEN RESPONSES

Aucta Pharmaceuticals, Inc.
Attention: Shoufeng Li
CEO
77 Suttons Lane
Pscataway, NJ 08854

Dear Mr. Li:[1]

Please refer to your pre-investigational new drug application (PIND) file for lacosamide extended-release capsules.

We also refer to your submission dated June 29, 2021, containing a meeting request. The purpose of the requested meeting was to seek advice from the Agency on the initial Pediatric Study Plan and to clarify expectations for the planned NDA submission.

Further reference is made to our Meeting Granted letter dated July 20, 2021, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your July 28, 2021, background package.

If you have any questions, call Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098 or email her at Stephanie.Parncutt@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, M.D.
Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

[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.

- Written Responses

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: PIND 140785

Product Name: Lacosamide extended-release capsules

Indication: Adjunctive therapy in the treatment of partial-onset seizures (b) (4)

Sponsor Name: Aucta Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Aucta plans to file its NDA application for its lacosamide extended-release capsule product following the 505(b)(2) regulatory pathway using Vimpat Tablets as the listed drug (LD) product. The sponsor has completed the manufacture of the registration batches and the single dose bioavailability/bioequivalence pharmacokinetic (PK) study between its product given once daily and the Vimpat immediate release (IR) tablet given twice daily. Registration stability is ongoing and steady state human PK study has been completed. A single dose food-effect study is planned.

The purpose of this meeting is to seek Agency's advice on its initial Pediatric Study Plan, submitted separately to the IND, and to clarify expectations for the planned NDA submission.

2.0 QUESTIONS AND RESPONSES

(b) (4)

[redacted] (b) (4)

We have recently determined that extrapolating the efficacy of drugs approved for the treatment of POS in adults to pediatric patients 1 month of age and older may be acceptable. Because the proposed LD is not labeled for use in pediatric patients 1 months to 4 years of age, your iPSP will need to address how you plan to evaluate the PK and safety of the proposed drug in this age group, if you seek to support efficacy through extrapolation. Additional discussion regarding the pediatric development of this product can occur once we have completed our review of the iPSP and provided our initial comments.

QUESTION 2: ***In this 505(b)(2) application, Aucta will reference the Agency's previous findings of nonclinical safety pharmacology and toxicology data for Vimpat® (lacosamide) Tablets, 50 mg, 100 mg, 150 mg, 200 mg, by UCB, Inc. Does the Agency agree that no other nonclinical studies are required for NDA submission and subsequent product approval?***

FDA Response

We agree that no additional nonclinical studies will be needed, provided that the clinical PK bridging data are considered adequate and there are no issues related to your formulation (e.g., excipients or impurities) that would require nonclinical safety assessment.

QUESTION 3: ***With the understanding that the indication would remain the same as Vimpat (lacosamide) tablets, 50 mg, 100mg, 150mg, 200mg, does the Agency agree that the safety and efficacy of the RLD is sufficient for filing of 505 (b)(2) NDA application for approval of Aucta's Extended Release Capsules, based on PK bridging? Does FDA agree that the below outlined studies would be sufficient to support a new modified release dosage form utilizing the abovementioned 505(b)(2) regulatory pathway?***

FDA Response

You could rely on the Agency's previous findings of efficacy and safety information from the LD if you demonstrate bioequivalence (BE) for the relevant pharmacokinetic parameters (e.g., Cmax, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}T}$) using the standard BE criteria (i.e., 90% confidence intervals of geometric mean ratios lying within 0.80 and 1.25) between your final to-be-marketed product and Vimpat Tablets as the LD. Any deviation from the standard BE criteria should be adequately justified. The adequacy of the studies will be a matter of review.

In addition, we have the following comment for the characterization of the lacosamide PK from the impact of food and sprinkle effect. For the labeling to indicate that the drug product can be sprinkled on soft foods, an in vivo relative bioavailability (BA) study should be performed by sprinkling the product on the soft foods to be listed in the labeling (test treatment) and comparing it to the product administered in the intact form (reference treatment),and then administering both on an empty stomach. Please refer to the Agency's draft Guidance for Industry entitled "Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations: Guidance for Industry" (February 2019) which is available at the following link https://www.fda.gov/media/121313/download

QUESTION 4: *Does the Agency agree that the dissolution method development and justification listed below are adequate?*

FDA Response

We cannot agree at this time because of the lack of details provided in the meeting package. Please provide the complete reports (for the dissolution method development and validation) with data and justifications in your NDA. Their adequacy and acceptability will be determined during the NDA review.

We note, however, based on the provided information, the following points for your consideration and/or implementation:

- The use of the 900 mL dissolution volume is not justified in view of the achievement of sink condition and similar drug release profiles to the (b) (4) mL volume.
- You should provide a listing of the critical material attributes (CMAs) and the critical process parameters (CPPs) affecting the dissolution of the proposed drug product (and, therefore, potentially the in vivo absorption/bioavailability) for the evaluation of the discriminating ability of the method.
- Based on the limited information presented and Figure 3 in the briefing package, it is not clear why other pH media (e.g., (b) (4) would not be suitable given the achievement of sink condition and similar and/or overlapping dissolution profiles.
- It is prudent to also investigate different stirring speeds in the (b) (4) mL dissolution volume to select the most suitable test condition/parameters.

QUESTION 5: *Based on FDA's guidance Waiver of In vivo BE studies, for Beaded capsules, in order to waiver lower strengths, f2 test using the recommended dissolution method discussed above is required. Tablet are required at least three dissolution media.*
Does the Agency agree that in-vivo studies for the lower strengths ((b) (4) 100 mg and 150 mg capsules) can be waived based on the below mentioned biowaiver studies?

FDA Response

We cannot agree at this time because of the lack of details provided in the meeting package. your overall proposed approach seems reasonable, except that multi-media comparative dissolution testing (i.e., pH (b) (4) with an f2 calculation will be necessary. With your NDA submission, please include a formal biowaiver request for the lower strengths not studied clinically and supportive information/data for our review.

QUESTION 6: ***Does the Agency agree that the below proposed in vitro alcohol dose dumping and soft-food studies are sufficient for NDA submission and subsequent product approval no other in-vitro dissolution studies are required in this area for the intended NDA?***

FDA Response

We cannot agree at this time because of the lack of details provided in the meeting package. Please refer to the response to Question 4. Since the proposed quality control (QC) dissolution medium is at pH 6.8 as presented in this meeting package, you will need to investigate the alcohol-induced dose-dumping potential in the pH 1.2 medium in addition to the proposed pH 6.8 medium (or one differing from pH 1.2). The Division of Biopharmaceutics does not have a specific requirement regarding the in vitro soft-feed studies. In view of the different pH dissolution media that you have proposed for the studies, we recommend that, at the time of NDA submission, you provide a rationale/justification for the selection of the testing conditions.

QUESTION 7: ***Can the Agency comment on the proposed in-process release and finished product specification (Table 5 and Table 6)?***

FDA Response

In general, the test parameters appear reasonable. The proposed acceptance limits and tests methods will be evaluated at the time of NDA review, when all of the data are available. At this time, we have the following comments regarding your proposed NDA submission:

1. We recommend testing of the (b) (4)
2. The proposed capsule formulation includes (b) (4)
3. Justify the proposed impurity/degradant acceptance limits that exceeds the respective ICH thresholds (e.g., Impurity (b) (4)
4. Provide complete elemental impurities risk assessment report.

We note the wider (b) (4) range limit at 3 hours and not less than (b) (4)% at (b) (4) hours for the proposed dissolution specifications (Table 6). In general, the selection of the dissolution acceptance criteria ranges is based on mean target value (b) (4)% and (b) (4)% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an established safe space based on an approved in vitro in vivo correlation (IVIVC) model, physiologically based biopharmaceutics modeling (PBBM), etc.

QUESTION 8: *We believe the above submission package is adequate for this 505(b)(2) NDA, can FDA comment on this?*

FDA Response

Please see all the responses to the previous questions. We have the following additional comments:

1. We recommend you refer to the ICH M4Q (R1) guideline for the format and information to be submitted in the NDA for drug substances and their corresponding drug products, available at: https://database.ich.org/sites/default/files/M4Q_R1_Guideline.pdf
2. Provide (b) (4)
3. Provide data for forced degradation and photostability studies of the proposed drug product.

(b) (4)

3.0 PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further

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

guidance on pediatric product development, please refer to FDA.gov.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

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.[6]

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.[7]

SECURE EMAIL COMMUNICATIONS

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[8]

MANUFACTURING FACILITIES

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[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[8] 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.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed

[9] https://www.fda.gov/media/84223/download

[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

for commercial production and those used for product and manufacturing process development.

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).[11] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[12]

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

[11] 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.
[12] http://www.regulations.gov

also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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

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

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

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the 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,* and the associated conformance guide, *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*.[13]

[13] 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/

NICHOLAS A KOZAUER
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