CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215025Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 149231

MEETING MINUTES

MAIA Pharmaceuticals, Inc.
Attention: Srikanth Sundaram, Ph.D.
Chief Scientific Officer
707 State Road
Suite 104; Princeton Gateway Building
Princeton, NJ 08540

Dear Dr. Sundaram:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sodium phenylacetate and sodium benzoate injection.

We also refer to the teleconference between representatives of your firm and the FDA on May 26, 2020. The purpose of this meeting was to discuss the proposed regulatory pathway and studies in your drug development program.

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

If you have any questions, contact Nicolas Kong, Regulatory Project Manager at Nicolas.Kong@fda.hhs.gov or 240-402-0269.

Sincerely,

{See appended electronic signature page}

Patroula Smpokou, M.D., FACMG
Deputy Director (Acting)
Division of Rare Diseases and Medical Genetics (DRDMG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA meeting

Meeting Date and Time: May 26, 2020 from 8:45 AM to 9:45 AM EST
Meeting Location: Teleconference

Application Number: 149231
Product Name: sodium phenylacetate and sodium benzoate injection.

Indication: hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle

Sponsor: MAIA pharmaceuticals, Inc.

Meeting Chair: Patroula Smpokou, M.D.
Meeting Recorder: Nicolas Kong, M.D.

FDA ATTENDEES

Division of Rare Diseases and Medical Genetics
Patroula Smpokou, M.D., FACMG, Deputy Director (acting)
Linda Jeng, M.D., Ph.D., FACMG, Clinical Team Leader (acting)
Sheila Farrell, M.D. Medical Officer

Division of Pharm/Tox of Rare Diseases, Pediatric, Urologic and Reproductive Medicine
Mukesh Summan, Ph.D., D.A.B.T., Director (acting)
Jackye Peretz, Ph.D., Toxicologist

Division of Regulatory Operations for Rare Diseases, Pediatric, Urologic and Reproductive Medicine
Pamela Lucarelli, Director, Project Management Staff
Nicolas Kong, M.D., Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Translational and Precision Medicine
Jie “Jack” Wang, Ph.D., Clinical Pharmacology Team Leader
Xiaohui “Michelle” Li, Ph.D., Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality
Donna Christner, Ph.D., API Branch Chief
Hong Cai, Ph.D., Drug Product Reviewer
Moo-Jhong Rhee, Ph.D., Drug Product Branch Chief
BreOnna DeLaine-Elias, Ph.D. Microbiology Reviewer
Neal Sweeney, Ph.D. Microbiology Reviewer

Joanne Wang
Kalpana Paudel, Ph.D., Biopharmaceutics reviewer
Vidula Kolhatkar, Ph.D., Biopharmaceutics Team Lead

SPONSOR ATTENDEES

Srikanth Sundaram, Ph.D. Chief Scientific Officer MAIA
Bikram Malik, Operations MAIA
Daniel Stewart, Product Development MAIA
John Alessandro, Technical Operations MAIA
Peter Grebow, Ph.D., Product Development Consultant to MAIA

1.0 BACKGROUND

The product sodium phenylacetate and sodium benzoate injection, is a sterile concentrated, aqueous solution of sodium phenylacetate and sodium benzoate supplied in a single-dose 20 mL vial. This product is being developed for the treatment of hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.

On April 1, 2020, the sponsor requested a meeting to discuss the proposed regulatory pathway and studies in their drug development program. The primary objectives of the meeting are to obtain agreement with the Agency on the proposed regulatory pathway and the adequacy of the proposed NDA for the final formulation selected for the registration batches and corresponding stability data proposal.

The meeting was granted as a type B meeting and a meeting request granted letter was issued on April 9, 2020. Preliminary comments were sent to the sponsor on May 22, 2020.

2. DISCUSSION

2.1. Administrative

Question 1: Given the differences in strength and fill volumes between MAIA's proposed product and the listed drug and given that a suitability petition addressing these differences has not been approved by FDA, does the Agency agree that the proposed application meets the requirements for a 505(b)(2) NDA?

FDA Response:
Yes, we agree that the 505(b)(2) regulatory pathway is the appropriate pathway for your proposed application. Refer to the 505(b)(2) Regulatory Pathway section below for additional information about submitting a 505(b)(2) NDA.

2.2. Chemistry, Manufacturing, and Controls

Question 2: Does the Agency concur with the proposed specifications for the two drug substances summarized in Table 2 and Table 3?

FDA Response:
The specifications appear reasonable for both APIs. A final determination will be made at the time of the application review.

Question 3: Does the Agency concur with the proposed specifications for the drug product?

FDA Response:
In general, your proposed specification for the drug product is reasonable. We would like to confirm that the proposed drug product specification includes two complementary Identification tests for EACH API per ICH Q6A. We also recommend that you add the following tests and acceptance criteria to the specification:

- (b) (4) the integrity of the container closure system;
- Elemental impurities;
- (b) (4);
- Meet the quality requirements of USP<1> for Injections.

For your NDA, the drug product specification should be based on the ingredients, solvents, manufacturing process, results of the stability tests of the registration and supportive batches, as well as ICH Guidelines Q6A. The drug product impurities should be listed in the specification table (categorized as specified, unspecified, and total impurities) and controlled per ICH Guidelines Q3B. The potential genotoxic impurities should be controlled per ICH M7. The elemental impurities should be controlled per USP <232>, USP <233>, and ICH Q3D. The (b) (4) should be controlled per (b) (4). Provide validated analytical methods used for the drug product release in accordance with ICH Guidelines Q2 and demonstrate that they are suitable for the intended use.

From the Product Quality Microbiology's perspective, the release specifications for the proposed drug appear reasonable. Please refer the following guidance: *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (1994).

The final determination will be made during the review of your NDA based on the totality of the data submitted in your NDA.

Meeting Discussion:

Following the Agency's preliminary written response, the Sponsor submitted a follow-up question to be discussed during the meeting:

Question 3a: Does the Agency agree with the proposal for inclusion of the three tests and specifications as detailed above in Table 2, and the confirmation of integrity of the container closure system through the (b) (4) during the batch manufacturing process?

During the meeting, the agency stated the following:

- **Your proposal seems reasonable, final determination will be done during NDA review.**
- **We remind you to provide the justification for the omission of the test of (b) (4) the container closure system integrity and the proposed risk-based assessment and justification for the control of elemental impurities and (b) (4) in the drug product specification.**

Question 4: Does the Agency concur with MAIA's proposal for stability data to be included in the NDA at the time of filing?

FDA Response:

Typically, a minimum of 12-month long term and 6 month accelerated stability data from three registration batches at the minimum of 1:10 of the intended commercial manufacturing scale using the same formulation, equipment, process and packaged in the same container closure system as proposed for marketing, at the proposed commercial manufacturing site are required per ICH guideline at the time of NDA filing. The stability data should be obtained with the drug product samples stored in two different orientations, such as upright and invert.

Alternatively, if you plan to submit 6-months of accelerated and long-term stability data from three registration batches and use the stability data from the approved ANDA 208521 to support this application at the time of this NDA filing, you should provide a letter of authorization allowing FDA to review the content of ANDA 208521. Further, you should demonstrate the proposed drug product is comparable to the approved ANDA 208521 with side by side comparation including the stability data between those two products. You should provide adequate justification and rationale that the proposed changes of the filling volume and the container and closure system in this drug product will not pose additional risk and concern to the drug product quality over its shelf life. We also remind you to include the extractable and leachable studies for the container and closure system as proposed for marketing and submit the results with appropriate risk assessment for detected extractable/leachable compounds. The final determination whether the proposed drug product is comparable to that of approved ANDA 208521 and its expiration dating period will be made during NDA review based on the totality of the data submitted in your NDA.

Meeting Discussion:

Following the Agency's preliminary written response, the Sponsor submitted two follow-up questions to be discussed during the meeting:
Question 4a. Does the Agency agree with MAIA's justification and rationale for the reduced stability database at the time of submission as outlined in Attachment 3 of the meeting package?

Question 4b. Does the Agency agree that extractable and leachable studies on the approved 50-mL ANDA product is supportive of the proposed 20-mL product?

- **The sponsor will provide a letter of authorization granting the FDA the right to review the content of ANDA 208521. At the time of NDA filing, the sponsor will provide the stability data obtained from ANDA 208521 with justification that the NDA subject drug product is supported by the same data.**
- **The sponsor committed to submit 9 and 12 months long-term stability data with the NDA. The sponsor believes that the information for the 9-month date will be available this month (May), and the 12-month data will be available in September 2020. FDA encouraged the sponsor to submit the results from those studies as soon as possible.**
- **The FDA stated that the proposed submission of 6-month stability data stored in two orientations (long-term and accelerated) from three production scale registration batches with the supporting stability data from ANDA 208521 at the time of NDA filing are acceptable. Final determination of the comparability of these two drug products and the assignment of expiration dating will be done at the time of the NDA review.**

2.3. Nonclinical

Question 5: Does the Agency agree that no nonclinical studies are needed given that the formulation of MAIA's proposed 20-mL product is identical to that of the listed drug and MAIA's approved 50-mL ANDA product?

FDA Response:
Yes, your proposal appears reasonable.

2.4. Clinical

Question 6: Does the Agency concur that no bioequivalence (pharmacokinetic) study is required to support the NDA?

FDA Response:
Your proposed drug product may qualify for a biowaiver request for a bioequivalence (pharmacokinetic) study. You will need to submit the following information to support a biowaiver request in your future NDA:

1. A side-by-side comparative table of the proposed drug product formulation and the reference drug product formulation.

2. Comparative physiochemical property data, such as pH and osmolarity of the proposed drug product formulation and the reference drug product formulation. The comparative data should be provided using at least 3 production lots, if available, of the proposed drug product, and 3 commercial lots of the reference drug product. The measurements should be done in triplicate for each lot tested.

The final determination on the acceptability of the waiver request, i.e. not to conduct a bioequivalence (pharmacokinetic) study, will be made during the NDA review process based on the totality of the provided data.

Meeting Discussion:
Following the Agency's preliminary written response, the Sponsor submitted a follow-up question to be discussed during the meeting:

Question 6a: Does the Agency concur that the available pH and osmolality data summarized in Table 1 above and comparison to MAIA's approved ANDA product are sufficient to justify granting a biowaiver?

During the meeting, the Agency reiterated that the sponsor's approach appears reasonable. Final determination on the biowaiver request will be made at the time of NDA review.

Question 7: Does the Agency agree that no additional studies are necessary to demonstrate that MAIA's product has the same clinical safety and efficacy as the listed drug AMMONUL?

FDA Response:
Yes, we agree.

2.5. General Questions

Question 8: Based on the NDA Table of Contents to be included in the Meeting Package, are there any other items that the Agency requires for filing and approval of the NDA?

FDA Response:
In your NDA, you should identify each nonclinical section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety for the listed drug and include a summary of the nonclinical data for each section that supports the

application. The adequacy of the nonclinical information provided to support approval will be determined at the time of the NDA review.

From the API standpoint, the proposed TOC for API and the plan to cross-reference Type II DMFs for the majority of the information and to provide the following information in the NDA is reasonable: Sections 3.2.S.1, 3.2.S.2.1, 3.2.S.3.2, 3.2.S.4, 3.2.S.5 and 3.2.S.7. Provide a Letter of Authorization to cross-reference both DMFs in your application.

The proposed drug product is a concentrated solution and must be diluted before intravenous administration. Therefore, an admixture study including the proposed drug product compatibility and the in-use stability study may be needed to support "The Dosage and Administration" (Section 2 of Prescribing Information).

From the product quality microbiology perspective, the NDA submission should include studies that demonstrate adventitious microbial contamination does not grow under the specified administration conditions of 24-hours at room temperature after dilution. Reference is made to Guidance for Industry: *ICH Q8 Pharmaceutical Development*, Section II.E and Guidance for Industry: *ICH Q1A(R2) Stability Testing of New Drug Substances and Products*, Section 2.2.7. Please include a description of the test methods and results of studies that are designed using a minimum countable inoculum ($\leq$100 CFU/mL) to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the population increases more than 0.5 $\log_{10}$, however other evidence of growth may be significant. Please perform the test using the storage conditions (temperature and duration) and diluents specified in product labeling. Please provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with nosocomial infection. Please provide a positive control that demonstrates the viability of the organisms over the duration of the test period.

From the drug product standpoint, you should update the submitted information accordingly based on the proposed drug product filled in 20 mL vial if you intend to use the information from the drug product (ANDA 208521) filled in 50 mL vial in support this NDA.

For preparation of the CMC sections in your NDA, refer to relevant CDER Pharmaceutical Quality/CMC Guidances and ICH Quality Guidelines located at the following websites as well as the USP Chapter. A final determination for the CMC related content and format included in the submission will be determined during NDA review.

- https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
- https://www.ich.org/page/quality-guidelines
- USP <1> Injections and Implanted Drug Products (Parenterals) – Product Quality Tests

From a clinical standpoint, the NDA Table of Contents seems reasonable. A final determination will be made during NDA review.

Meeting Discussion:
Following the Agency's preliminary written response, the Sponsor submitted a follow-up question to be discussed during the meeting:

Question 8a. Can the Agency clarify its request to "update the submitted information accordingly"?

If the information from ANDA 208521 (50-mL vial) will be used in supporting CMC sections of this NDA submission, the sponsor was asked to update those contents and provide the justification based on the requirements of the proposed 20-mL vial configuration. Further, the applicant should provide the locations of the specific information in ANDA 208521.

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.

Because none of the criteria apply at this time to your application, 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.

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).[1] 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.[2]

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

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

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

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug

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

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.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor responses to preliminary comments.

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

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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/

NICOLAS KONG
06/18/2020 09:55:45 AM
Signed on behalf of Patroula Smpokou