CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215025Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215025
Assessment 1

Drug Product Name	Sodium phenylacetate and Sodium benzoate Injection
Dosage Form	Injection
Strength	10%/10% [2 g/20 mL; 2 g/20 mL]
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	MAIA Pharmaceuticals, Inc., Princeton, NJ
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Aug 21, 2020	OPQ
Amendment	Sep 24, 2020	ONDP, Drug Product
Amendment	Jan 26, 2021	OPQ, Microbiology
Amendment	Feb 26, 2021	ONDP, Drug Product
Amendment	Apr 9, 2021	ONDP, Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Gaetan Ladouceur	Donna Christner,
Drug Product	Zhengfang Ge	Wendy Wilson
Manufacturing	Yan Xu	Joanne Wang
Microbiology	BreOnna DeLaine-Elias	Neal J. Sweeney
Biopharmaceutics	Bryan Ericksen	Vidula Kolhatkar
Regulatory Business Process Manager	Oumou Barry	
Application Technical Lead	Hitesh Shroff	
Laboratory (OTR)	N/A	
Environmental	Zhengfang Ge	Wendy Wilson

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Active	Last reviewed by the Agency on Sep 18, 2020 (Adequate).	LOA: May 14, 2020
	II			Active	Last reviewed by the Agency on Sep 18, 2020 (Adequate).	LOA: Jul 23, 2020
	III			Active	Not reviewed, Information provided in NDA	LOA: Jun 9, 2020
	III			Active	Not reviewed, Information provided in NDA	LOA: Aug 6, 2020

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
ANDA	208521	MAIA Pharma. Inc.; Sodium phenylacetate and Sodium benzoate Injection, 10%, 10% (5g/50mL, 5g/50mL) LOA: Aug 14, 2020

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Sodium phenylacetate and Sodium benzoate Injection, 10%/10% (2g/20mL;2g/20mL).

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall "Approval" recommendation for the facilities involved in this application.

The label/labeling is satisfactory from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for "**Approval**".

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Sodium phenylacetate and Sodium benzoate Injection, 10%/10% (2g/ 20mL; 2g/ 20mL) is a sterile, concentrated, nonpyrogenic, clear and almost colorless aqueous solution of sodium phenylacetate and sodium benzoate. It is intended for intravenous administration via a central venous catheter only after dilution with sterile 10% Dextrose Injection (D10W). Each mL of Sodium phenylacetate and Sodium benzoate Injection contains 100 mg of sodium phenylacetate and 100 mg of sodium benzoate, and Water for Injection. Its pH may be adjusted to 7.5 and (b) (4) with either sodium hydroxide or hydrochloric acid. There are no preservatives or antioxidants in this formulation.

Ammonul (sodium phenylacetate and sodium benzoate) injection, 10%/10% (5g/ 50mL; 5g/ 50mL) was approved in 2005 (Bausch Health US LLC., NDA 020645). The proposed drug product has different size (20 mL) and strength (2g/20mL; 2g/20mL) compared to Ammonul Injection.

Proposed Indication(s) including Intended Patient Population	Indicated as adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.
Duration of Treatment	As needed
Maximum Dose	The dose is weight dependent - from 2.5 mL/kg to 55 mL/m^2
Alternative Methods of Administration	N/A

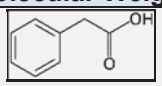
B. Quality Assessment Overview

Drug Substance: Adequate

The drug substances in Sodium phenylacetate and Sodium benzoate Injection, 10%/10% (2g/ 20mL; 2g/ 20mL) are Sodium phenylacetate and Sodium benzoate.

Sodium phenylacetate is a white to off-white powder, it is freely soluble in water and alcohol. It is very hygroscopic. Sodium benzoate is a white (b) (4) powder. It is soluble in water. It is slightly hygroscopic.

The detailed CMC information including physicochemical properties, manufacturing process, characterization, specification, Certificate of Analysis, container closure system and stability of both drug substances is provided in the DMFs from their manufacturers. The letters of authorization were provided. The DMFs were reviewed and deemed adequate.

Drug Substances	Structure Chemical formula Molecular Weight	DMF #	Holder	Date Assessment Completed
Sodium phenylacetate	 $C_8H_7O_2Na$ 158.3		(b) (4)	Last reviewed by the Agency on Sep 18, 2020 (Adequate).
Sodium benzoate	$C_6H_5CO_2Na$ 144.10			Last reviewed by the Agency on Sep 18, 2020 (Adequate).

A (b) (4)-month retest period for Sodium phenylacetate and Sodium benzoate is supported by their stability study results.

The CMC information was reviewed by the drug substance reviewer and concluded that the submitted information is adequate to support the drug product. (see the **Drug Substance** review)

Drug Product: Adequate

Sodium phenylacetate and Sodium benzoate Injection, 10%/10% (2g/ 20mL; 2g/ 20mL) is a sterile aqueous solution of sodium phenylacetate and sodium benzoate with pH 7.5 to (b) (4). There are no preservatives or antioxidants in the drug product formulation. It is intended for intravenous administration only after dilution with sterile 10% Dextrose Injection (D10W).

The drug product is supplied as single-dose 20mL clear USP (b) (4) glass vials, closed with a grey 20 mm (b) (4) rubber stoppers and sealed with a 20 mm aluminum flip-off caps.

The drug product specification includes the following tests: visual description, identification by UV and HPLC, pH, volume in container per USP <697>, particulate matter per USP <788>, sterility per USP <71>, bacterial endotoxin per USP <85>, assay of sodium benzoate and sodium phenyl acetate by HPLC, related substance by HPLC and osmolality per USP <785>. The elemental impurities comply with USP <232> and ICH Q3D requirements based on the risk assessment. All in-house developed, non-compliant analytical methods were validated per ICH Q2 (R)(1).

The Sodium phenylacetate and Sodium benzoate Injection compatibility study was conducted with 10% Dextrose and Arginine Hydrochloride Injection, 10%. For the compatibility study the following key attributes were assessed: description, pH, assay of sodium benzoate and sodium phenyl acetate, impurities, color of the solution, particulate matter, sub-visible particles, visible particles and osmolality. The results from generic RLD and the proposed drug product are virtually the same.

Based on the satisfactory long-term and accelerated stability studies in upright and inverted positions on three primary registration batches of the drug product, the proposed **24-month of expiration dating period** is granted when it is stored at 25°C in the proposed container closure system. (see the **Drug Product** review)

Labeling: Adequate

The proposed label/labeling is adequate from the CMC perspective. (see the **Labeling Review)**

Manufacturing: Adequate

The drug product is manufactured by Gland Pharma Ltd., India by a typical injection manufacturing process. The key steps in the drug product manufacturing (b) (4)

At appropriate steps during the drug product manufacturing process, in-process controls for dissolution of drug substances, pH of bulk solution, bacterial Endotoxin test of bulk solution before and after storage, fill volume check, optical inspection and visual inspection of the filled vials were established.

MAIA provided a flow diagram and a detailed drug product manufacturing process describing incoming materials, unit operations, critical steps, in-process controls, process parameters and equipment used.

The drug product manufacturing process, in-process controls, drug product release tests and executed batch records were reviewed and deemed satisfactory from the OPMA perspective. (See the **Manufacturing Integrated Assessment**)

Facilities: Adequate

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall "Approval" recommendation for the facilities involved in this application.

Environmental Assessment: Adequate

MAIA Pharmaceuticals, Inc. submitted a claim of categorical exclusion from the requirement of an Environment Assessment (EA) statement. Based on the statement of no extraordinary circumstances exists, the claim of categorical exclusion is accepted. (see the **Drug Product** Review)

Biopharmaceutics: Adequate

Both sodium phenylacetate and sodium benzoate can be considered high solubility Biopharmaceutics Classification System (BCS) Class I or III compounds. No bridging of formulations is necessary. The Applicant provided a side-by-side comparison of formulations and pH and osmolality data to compare the proposed product with the listed drug, Ammonul. These data are adequate and a biowaiver can be granted according to 21 CFR 320.24(b)(6). The biopharmaceutics reviewer concluded that the applicant has provided adequate information therefore from a biopharmaceutics perspective this NDA is recommended for approval. (see the **Biopharmaceutics** review)

Microbiology: Adequate

(b) (4)

as well as the microbiology related attributes of the drug product specification including, antimicrobial effectiveness testing, bacterial endotoxins, sterility, container closure integrity, post-marketing stability protocol and commitment as well as PI were reviewed. This NDA is recommended for approval based on drug product sterility assurance from the microbiological perspective. (See the **Microbiology** review)

Lifecycle Management Considerations: None

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
Particulate Matter, sub-visible particles, precipitates in the drug product	Manufacturing process, filling, storage	L	(b) (4)	No precipitates were observed and Particulate matter remained within acceptable range during the admixture in-use stability testing. **Acceptable**	None
Bioburden	Manufacturing environment and processes	L		Bioburden is controlled in the drug product at release and stability. Bacterial Endotoxins controlled per USP <71> in release and stability specification. **Acceptable**	None
Sterility	(b) (4)	L		Drug product sterility is controlled per USP <71> at release and stability **Acceptable**	None

D. List of Deficiencies for Complete Response: None

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products II
May 10, 2021

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The proposed prescribing information is deemed ADEQUATE. The NDA is recommended for approval from the labeling perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**Not proposed**	
Established name(s)	**SODIUM PHENYLACETATE and SODIUM BENZOATE**	Adequate
Route(s) of administration	**Injection, for intravenous use**	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: 10% per 10% sterile, concentrated, aqueous solution of sodium phenylacetate and sodium benzoate.	Adequate Same as the listed drug
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Same as the listed drug

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Provided same as the listed drug product	**Adequate**

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

Sodium Phenylacetate and Sodium Benzoate Injection 10% per 10% is a sterile, clear and almost colorless concentrated, aqueous solution of sodium phenylacetate and sodium benzoate.

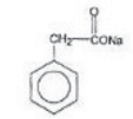
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	**Adequate**
Strength(s) in metric system	10% per 10%	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	active ingredients are sodium phenylactate and sodium benzoate	**Adequate** Per Agency guidance for "Naming of Drug Products Containing Salt Drug Substances, the proposed drug product should be named as salt to maintain consistency as the listed drug product AMMONUL, as an exception USP salt does not apply
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	sterile, clear and almost colorless concentrated, aqueous solution	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	sterile, concentrated, aqueous solution	**Adequate** Same as the listed drug

1.2.3 Section 11 (DESCRIPTION)

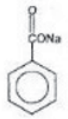
11 DESCRIPTION

Sodium Phenylacetate and Sodium Benzoate Injection 10% per 10% (a nitrogen binding agent) is a sterile, concentrated, aqueous solution of sodium phenylacetate and sodium benzoate. The pH of the solution is between 7.5 and 8.3. Sodium phenylacetate is a white to off-white powder. It is soluble in water. Sodium benzoate is a white to off-white powder that is readily soluble in water.

Figure 1



Sodium Phenylacetate



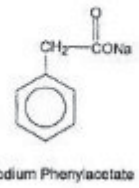
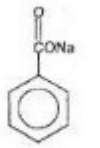
Sodium Benzoate

Sodium phenylacetate has a molecular weight of 158.14 and the molecular formula $C_8H_7NaO_2$. Sodium benzoate has a molecular weight of 144.10 and the molecular formula $C_7H_5NaO_2$.

Each mL of Sodium Phenylacetate and Sodium Benzoate Injection contains 100 mg of sodium phenylacetate and 100 mg of sodium benzoate, and Water for Injection. Sodium hydroxide and/or hydrochloric acid may have been used for pH adjustment.

Sodium Phenylacetate and Sodium Benzoate Injection is a sterile, concentrated solution intended for intravenous administration via a central venous catheter only after dilution *[see Dosage and Administration (2)]*.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Sodium Phenylacetate and Sodium Benzoate	**Adequate**
Dosage form(s) and route(s) of administration	Injection Intravenous administration via a central venous catheter only after dilution	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	not apply	**Adequate** **To be consistent with the approved drug**
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Water for Injection. Sodium hydroxide and/or hydrochloric acid may have been used for pH adjustment.	**Adequate**
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	100 mg of sodium phenylacetate and 100 mg of sodium benzoate, and Water for Injection. Sodium hydroxide and/or hydrochloric acid may have been used for pH adjustment.	**Adequate**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	**Adequate**
Statement of being sterile (if applicable)	Sterile	**Adequate**
Pharmacological/ therapeutic class	nitrogen binding agent	**Adequate**

Chemical name, structural formula, molecular weight	Sodium phenylacetate has a molecular weight of 158 (b) (4) and the molecular formula C8H7NaO2.  Sodium Phenylacetate Sodium benzoate has a molecular weight of 144 (b) (4) and the molecular formula  Sodium Benzoate C7H5NaO2.	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	The pH of the solution is between 7.5 and 8.3…	**Adequate**

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING

Sodium Phenylacetate and Sodium Benzoate Injection 10% per 10% is clear and almost colorless solution supplied in a sterile, non-pyrogenic, single-dose glass vial.

NDC 70511-101-20 single-dose vial containing 20 mL of Sodium Phenylacetate and Sodium Benzoate Injection 10% per 10%.

Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Injection	**Adequate**
Strength(s) in metric system	10% per 10%	**Adequate**
Available units (e.g., bottles of 100 tablets)	single dose vial containing 20 mL	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	clear and almost colorless solution supplied in a sterile, non-pyrogenic, single-dose glass vial NDC provided	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose glass vial	**Adequate**
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	None	**Adequate**
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)	**Adequate**
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: MAIA Pharmaceuticals, Inc. 707 State Road, Suite 104 Princeton, NJ 08540	**Adequate**

2.0 PATIENT LABELING

N/A

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (blister wallet)

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Sodium Phenylacetate and Sodium Benzoate Injection	**Adequate**
Dosage strength	10%/10%	**Adequate**
Route of administration	For IV use only	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	not apply	**Adequate** To be consistent with the approved drug per Agency's guidance
Net contents (e.g. tablet count)	20 mL	**Adequate**
"Rx only" displayed on the principal display	Provided	**Adequate**
NDC number	Provided	**Adequate**
Lot number and expiration date	Provided	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	**Storage: Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).**	**Adequate**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single dose vial	**Adequate**
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	**Must be diluted before IV administration.** Sterile, non-pyrogenic, single-dose vial.	**Adequate**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	**Adequate**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	**Manufactured for:** MAIA Pharmaceuticals, Inc. Princeton, NJ 08540 **Manufactured by:** Gland Pharma, Ltd. Hyderabad, India	**Adequate**
Medication Guide (if applicable)	**Dosage: See accompanying package insert.**	**Adequate**
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	Each mL contains: 100 mg of sodium phenylacetate and 100 mg of sodium benzoate, and Water for Injection. Sodium hydroxide and/or hydrochloric acid may have been used for pH adjustment. Sterile, concentrated solution must be diluted with sterile, dextrose injection, 10% (D10W) before intravenous administration.	**Adequate**

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

None

Overall Assessment and Recommendation:

The NDA is ready for approval per CFR 314.125(b)(6)

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson, Ph. D.
Director/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Date: 4/12/2021 01:41:03PM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 4/12/2021 02:24:39PM
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BIOPHARMACEUTICS

Product Background:

The current submission is for the approval of Sodium Phenylacetate and Sodium Benzoate Injection. Sodium Phenylacetate and Sodium Benzoate are indicated as adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.

NDA-215025-ORIG-1

Drug Product Name / Strength: Sodium Phenylacetate and Sodium Benzoate / 10%/10% [2g/20 mL; 2g/20 mL]

Route of Administration: Intravenous injection

Applicant Name: MAIA Pharmaceuticals, Inc.

Primary Biopharmaceutics Reviewer Name: Bryan Ericksen, Ph.D.

Secondary Reviewer Name: Vidula Kolhatkar, Ph.D.

Review Summary: Adequate

Both sodium phenylacetate and sodium benzoate can be considered high solubility Biopharmaceutics Classification System (BCS) Class I or III compounds. No bridging of formulations is necessary. The Applicant provided a side-by-side comparison of formulations and pH and osmolality data to compare the proposed product with the listed drug (LD), Ammonul. These data are adequate and a biowaiver can be granted according to 21 CFR 320.24(b)(6). NDA 215025 is adequate from a biopharmaceutics perspective.

Submission being reviewed:

08/21/2020	NDA 215025/Sequence 0001/Original Submission

BCS Designation

Reviewer's Assessment: Both sodium phenylacetate and sodium benzoate can be considered high solubility (BCS Class I or III) compounds.

Solubility:

Sodium phenylacetate:

Freely soluble (1 gram in 1-10 mL) in water (pH 2, 4, 7, 9, and 12).
Freely soluble in methanol and ethanol.
Practically insoluble in isopropyl alcohol, acetone, and ethyl acetate.

Sodium benzoate:

0.55 g/mL in water. Freely soluble in water.
Soluble in ethanol (90% v/v).
Sparingly soluble in an alcohol.
>540 mg/mL to <560 mg/mL in 0.2 M Phosphate buffer at pH 6.0 to 8.0 at 20-25ºC

Permeability:

The Applicant did not provide permeability information. However, phenylacetate is freely permeable in various tissues of the rat (Loo YH, Fulton T, Wisniewski HM. Vulnerability of the immature brain to phenylacetate intoxication: tissue permeability to phenylacetate. J Neurochem. 1979 Jun;32(6):1697-8). Therefore, it is likely that phenylacetate is a BCS Class I compound (high solubility, high permeability). Permeability is not pertinent because the proposed product is an intravenous injection.

Dissolution:

The drug product is a solution for injection, so the Applicant did not provide dissolution information.

Bridging of Formulations

Reviewer's Assessment: Adequate

The formulation is the same as ANDA 208521 for the 50-mL generic product, which was approved 05/08/2017. Because the formulation was not modified during product development, no bridging of formulations is necessary.

Biowaiver Request

The Applicant submitted a request for biowaiver under 21 CFR320.22(b)(1), 21 CFR 320.22(d)(3), and/or 21 CFR 320.24(b)(6).

The LD is Ammonul injection (sodium phenylacetate and sodium benzoate 10%/10% [5 g/50 mL; 5 g/50 mL], NDA 020645, which was approved 02/17/2005.

The proposed 505(b)(2) 20-mL product contains the same active and inactive ingredients at the same concentrations as the listed drug and MAIA's approved generic 50-mL product (ANDA

208521), but with a lower amount of active pharmaceutical ingredient (2 g each per 20 mL) and fill volume (20 mL) as compared to the listed drug (5 g each per 50 mL).

A side-by-side comparison of the proposed product, LD, and approved generic 50-mL product are given in Table 1.

Table 1: Comparison of MAIA's Proposed 505(b)(2) NDA Product versus the Listed Drug and MAIA's Approved ANDA Product

AMMONUL (Sodium Phenylacetate and Sodium Benzoate) Injection 10%/10% in a 50 mL vial		MAIA's Sodium Phenylacetate and Sodium Benzoate Injection, 10%/10%		
			50 mL Approved ANDA Product	20 mL Proposed 505(b)(2) Product
Ingredient	**Amount (mg/mL)**	**Ingredient**	**Amount (mg/mL)**	**Amount (mg/mL)**
Sodium Phenylacetate (mg)	100	Sodium Phenylacetate (mg)	100	100
Sodium Benzoate (mg)	100	Sodium Benzoate (mg)	100	100
Sodium Hydroxide, NF	q.s. (pH 6 to 8)*	Sodium Hydroxide, NF	q.s. (pH 7.5-8.3)	q.s (pH 7.5-8.3)
Hydrochloric Acid, NF		Hydrochloric Acid, NF		
Water for Injection, USP	q.s. to 50 mL	Water for Injection, USP	q.s. to 50 mL	q.s. to 20 mL

* (b) (4) q.s. = quantity sufficient

Note that because of rounding error of the pH 6 to 8 range of the LD, (b) (4)

Physicochemical properties of the proposed product, LD and approved generic product are given in Table 2.

Table 2: Comparison of pH and Osmolality Data for Reference Drug product, MAIA's Approved 50-mL ANDA Product, and its Proposed 20-mL 505(b)(2) NDA Product

Drug Product Description	Lot #	pH	Osmolality (1:10 dilution in WFI†) mOsmol/kg
Reference Drug (AMMONUL Injection, 5 g/50 mL; 5 g/50mL)	2337-105	7.8	255
MAIA 50-mL ANDA Product (5 g/50 mL; 5 g/50mL	(b) (4) 401	7.8	253*
	402	7.7	249*
	403	7.7	252*
	601	7.7	271
	802	7.8	270
	901	7.6	263
MAIA Proposed 20-mL NDA Product (2 g/50 mL; 2 g/50mL	901	7.7	263
	902	7.9	266
	903	7.8	268

† The drug product is a highly concentrated solution with a theoretical osmolality of 2653 mOsmol/kg and must be diluted to measure osmolality using conventional osmometers that rely on freezing point depression
* Data generated during ICH stability program at approximately 17 months after manufacture

Reviewer's Assessment: Adequate

Both pH and osmolality are comparable to the LD. These data are adequate and a biowaiver is granted according to 21 CFR 320.24(b)(6).

Bryan Ericksen

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Vidula Kolhatkar

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Date: 5/04/2021 03:05:04PM
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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Sodium Phenylacetate and Sodium Benzoate is indicated as an adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia.
NDA Number	215025
Assessment Cycle Number	1
Drug Product Name/ Strength	Sodium Phenylacetate and Sodium Benzoate Injection, 10%/10%; Sodium Phenylacetate 2 g and Sodium Benzoate 2 g in 20 mL per vial
Route of Administration	Intravenous Injection
Applicant Name	MAIA Pharmaceuticals, Inc. 707 State Road Suite 104; Princeton Gateway Building Princeton, NJ 08540
Therapeutic Classification/ OND Division	Antimetabolite
Manufacturing Site	Gland Pharma Limited Survey No. 143-148, 150 & 151 Near Gandimaisamma Cross Roads, D.P. Pally, Dundigal - Gandiamaisamma Mandal, Medchal - Malkajgiri District, Hyderabad, 500 043, Telengana, India
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary**:** The submission **is recommended** for approval on the basis of sterility assurance.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SN 0001	08/21/2020
SN 0002	09/24/2020
SN 0006	01/29/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A. This is a first cycle review.

Remarks: The applicant currently markets a generic version of the proposed drug product, Sodium Phenylacetate and Sodium Benzoate Injection, in a 50 mL fill volume, under approved ANDA 208521. The subject NDA has the same composition and manufacturing process as the approved ANDA drug product. The reference listed drug for the approved ANDA is AMMONUL (sodium phenylacetate and sodium benzoate) Injection, 10% per 10% under NDA 020645 held by Bausch Health Companies, Inc., Bridgewater, NJ.

Concise Description of Outstanding Issues: None.

Supporting Documents:

- Microbiology review A208521MR01 dated July 29, 2016 (adequate) for the review of ANDA 208521, the generic version of the proposed drug product in 50 mL/20 mm vials.
- Pre-IND 148231 microbiology memo dated May 26, 2020 for Agency feedback regarding the submission of the subject NDA.
- Letter of authorization dated June 9, 2020 from (b) (4) referring to DMF (b) (4) for information regarding the 20 mm stoppers ((b) (4)).
- Microbiology review D(b) (4)M54R01 dated November 30, 2020 for the (b) (4) rubber stopper (b) (4) validation data at the (b) (4) facilities.

S DRUG SUBSTANCE

Assessment: *N/A*

The drug substance is not sterile; therefore, the API information is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** The drug product is a sterile, clear and almost colorless aqueous solution.

- **Drug product composition –**

Ingredient, Quality Standard	Function	Quantity / mL
Sodium phenylacetate, In-house	Active Ingredient	100 mg
Sodium benzoate, NF	Active Ingredient	100 mg
Sodium hydroxide, NF	Alkalizing agent	q.s. for pH adjustment to 7.5 to 8.0
Hydrochloric acid, NF	Acidifying agent	
Water for injection, USP	Solvent	q.s. to 1.0 mL
(b) (4)		

- **Description of container closure system –**

Configuration	Component	Description	Manufacturer
20 mL fill	Container	20 mL USP Type (b) (4) glass vial with 20 mm neck	(b) (4)
	Closure	20 mm grey (b) (4) rubber stopper	
	Seal	20 mm aluminum flip off seals	

Three exhibit batches ((b) (4)901, (b) (4)902, (b) (4)903) were manufactured in April 2019. Each exhibit batch was (b) (4) L, the same size as the proposed commercial batches.

Assessment: *Adequate*

The information provided in the application adequately describes the drug product and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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MICROBIOLOGY LIST OF DEFICIENCIES

NDA: 215025 APPLICANT: MAIA Pharmaceuticals, Inc.

DRUG PRODUCT: Sodium Phenylacetate and Sodium Benzoate Injection

There are currently no deficiencies identified based on the information submitted.

Primary Microbiology Assessor Name and Date:
BreOnna DeLaine-Elias, Ph.D.
Microbiologist
CDER/OPQ/OPMA/DMA 1/Branch 2
February 4, 2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Neal J. Sweeney, Ph.D.
Senior Pharmaceutical Quality Assessor
CDER/OPQ/OPMA/DMA 1/Branch 2
February 4, 2021

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/

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