

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216395Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

TO: File for NDA 216395

FROM: Vanesa C Sanchez
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Office of Cardiology, Hematology, Endocrinology, & Nephrology (OCHEN)

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Team Lead, DPT-CHEN, OCHEN

DATE: 01/13/2026

SUBJECT: SDN 01 and 07

CMP Development, LLC submitted NDA 216395 (IND 144328) for QUIOFIC Folic Acid Oral Solution (1 mg/ 5 mL) as a 505(b)(2) application for the treatment of megaloblastic anemias due to a deficiency of folic acid and anemias of nutritional origin, pregnancy, infancy, or childhood. The recommended starting dosage in adults and pediatric patients (regardless of age) is up to 1 mg orally daily.

The Nonclinical Team received consultation requests from the CMC Teams, Dr. Parvin Akther from OPQAI/DPQAI and Dr. Mitchell McCloskey from OPQAIII/DPQAXI, to evaluate the acceptance of the proposed limits for the specified flavor ingredients, impurities, degradants, extractables, and leachables in drug product (DP) and impurities in drug substance (DS).

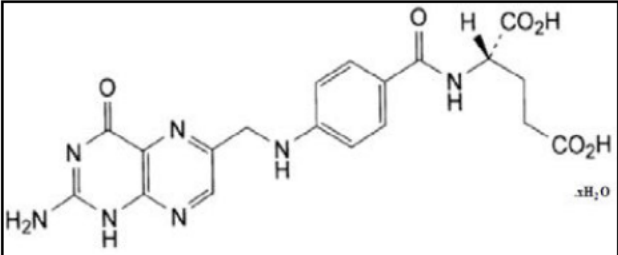
This memo encompasses the analysis performed to respond the CMC Consult requests.

Division Assessment and Conclusions

There were no identifiable safety issues from a nonclinical perspective. The levels of excipients in the Mixed Berry Flavor (b) (4) (listed on DMF (b) (4)) and of the impurities in the DS and DP are acceptable based on lack of mutagenicity potential, available supporting toxicological data, and proposed dosage administration.

Nonclinical Summary

Drug Information

Type of Product:	Small molecule
Code/ Generic Name:	Folic Acid
Chemical Name (optional):	N-[4-[[2-amino-1,4-dihydro-4-oxo-6-pteridiny]methyl]amino]benzoyl]-L-Glutamic acid
CAS# or UNII (if available):	CAS:59-30-3 UNII:935E97BOY8
Structure or Biochemical Description:	
Molecular Formula/ Molecular Weight:	C ₁₉ H ₁₉ N ₇ O ₆ · xH ₂ O/ 441.4 g/mol
Comment on Excipients:	Drug product (DP) formulation has a new flavor composition not previously used in the US. (b) (4) – Mixed Berry Flavor. (b) (4)
Comment on Impurities:	The process impurity (b) (4) exceeds the Q3B (R2) recommended limit at (b) (4) a NMT (b) (4) % limit established by the Sponsor ((b) (4) μg)
Proposed 505(b)(2): If Yes, Listed Drug:	Y Folvite (NDA 080680-Discontinued); Folic Acid 1 mg Tablets (ANDA 040625)
Biosimilar: If Yes, Reference Product:	N N/A

Relevant INDs, NDAs, BLAs or DMFs

There have been a number of INDs for folic acid. Refer to Appendix-**Error! Reference source not found.** for details on active/approved applications.

Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
IND 144328	Wentao Fu	12/13/2019	Clin Pharm Review.
	Suria Yesmin	11/26/2019	Meeting Minutes

Drug Information

Drug Formulation

The inactive ingredients in Quiofic Folic Acid Solution formulation are below the previously used in approved drugs as described in the inactive ingredient drug (IID) FDA Database¹ for the oral route (Table 1).

Table 1. Quiofic Folic Acid Solution Composition

Ingredient	Q.S.	Function	% w/v	Quantity/ (mg/5 mL)	IID limit from FDA Database for Oral Route	
					MPpUD (mg)	MDA (mg in formulation)
Folic Acid	USP	API	0.02	1.00		
Sodium Phosphate Monobasic, (b) (4)	USP	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sodium Phosphate Dibasic, (b) (4)	USP					
Propylene Glycol ^A	USP					
Edetate Disodium	USP					
Methylparaben	NF					
Propylparaben	NF					
Sorbitol Solution (b) (4) A	USP					
Mixed Berry Flavor, (b) (4) b	N/A					
Purified Water	USP					
Total						

^A [Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol Guidance for Industry \(2023\)](#)

^B [Evaluating Color Additives and Flavors Intended for Oral Drug Products Submitted or Referenced in INDs and NDAs \(MaPP 5021.2; 2021\)](#)

Q.S.= Quality Standard; MPpUD= Maximum Potency per unit dose ; MDA= Maximum daily exposure; IID= inactive ingredient drug

Drug Excipients

Mixed Berry Flavor, [REDACTED] (b) (4)
 [REDACTED]
 [REDACTED]

¹ [Inactive Ingredient for Approved Drug Products \(IID\)](#)

² [M7\(R2\) Assessment and Control of DNA Reactive \(Mutagenic\) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk Guidance for Industry. 2023](#)

Reviewer assessment: No safety concerns were identified in the ingredient composition of the Mixed Berry Flavor formulation from a nonclinical perspective. The individual components present above the proposed 1.5 µg threshold per M7(R2) have adequate data describing chemical name, quantitative composition (amount per unit basis), CAS number, quality standard, and generally recognized as safe (GRAS) designation by the Code of Federal Regulation (CFR) with available reference; with the exception of (b) (4) with only available reference to the CFR and no designation.

The conducted nonclinical assessment followed the Manual of Policies And Procedures (MAPP) 5021.2³: Refer to Appendix-Table 5 for details and toxicological information

Drug Impurities

For a complete list and details of impurities in DS and DP refer to Appendix - Table 6.

In DP:

- Degradant: (b) (4) – proposed limit is NMT (b) (4) (meets ICH Q3B limit)
- Extractables: No extractable are found above analytical evaluation threshold (AET) for bottle and cap. Two extractables compounds (b) (4) identified in the (b) (4) are above AET (b) (4) µg/mL.
 - 1) (b) (4)
 - 2) (b) (4)
- Leachables: Leachable studies are performed on initial and 15 months drug product samples; no compounds are observed above AET.

Reviewer assessment: Potential qualifying impurities present in DS and DP, as determine on thresholds referenced in Q3A(R2)⁴ and Q3B(R2)⁵, respectively, are not predictive to be mutagenic based on (Q)SAR M7 analysis, thus they are considered acceptable from a nonclinical perspective. Refer to Appendix - Table 6 and Computational Toxicology Consult: (Q)SAR Report for assessment details.

³ [MAPP 5021.2. CDER. Office Of Pharmaceutical Quality. Evaluating Color Additives and Flavors Intended for Oral Drug Products Submitted or Referenced in INDs and NDAs.](#)

⁴ [Guidance for Industry Q3A\(R\) Impurities in New Drug Substances \(ICH 2008\)](#)

⁵ [Guidance for Industry Q3B\(R2\) Impurities in New Drug Products \(ICH 2006\)](#)

Appendix/Attachments

Approved and Active applications with Folic Acid.

- Up-to-date active and approved applications related to folic acid DP are listed in Table 2.
 - Highlighted in green are:
 - the RLD Folvite Tablets, 1 mg manufactured by Wyeth Pharmaceuticals Inc (NDA 005897; approved in 06/05/1947);
 - the RS Folic Acid Tablets, 1 mg, supplied by Amneal Pharmaceuticals (ANDA 040625; approved in 07/21/2005),
 - Highlighted in blue are the Folic Acid applications by the CMC Development (Sponsor).

Table 2. Relevant Folic Acid Applications

Application Type/Number	Application SubType	Product Name	Submitter	Dosage Form	Responsible Organization	Current Status	Status Date	Indication/Subject/Issue
IND-								(b) (4)
IND-								
IND-								
ANDA-202522	Unknown	Folic Acid	XGEN PHARMACEUTICALS DJB INC	INJECTION	CDER/OGD	Approved	11/06/2019	Treatment of megaloblastic anemias due to deficiency of folic acid as may be seen in tropical or nontropical sprue, in anemias of nutritional origin, pregnancy, infancy or childhood. n/a
ANDA-211064	Unknown	Folic Acid	ATHEM HOLDINGS LLC	TABLET	CDER/OGD	Approved	03/08/2019	Folic acid, USP is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid, USP (as may be seen in tropical or nontropical sprue) and in anemias of nutritional origin, pregnancy, infancy, or childhood.
ANDA-204418	Unknown	Folic Acid	NUVO PHAMACEUTICALS INC	TABLET	CDER/OGD	Approved	07/28/2015	Indicated for the treatment of megaloblastic anemias due to a deficiency of folic acid and in anemias of nutritional origin, pregnancy, infancy, or childhood...
ANDA-202437	Unknown	Folic Acid	CADILA PHARMACEUTICALS LTD	TABLET	CDER/OGD	Approved	01/27/2014	treatment of megaloblastic anemias due to a deficiency of folic. n/a
ANDA-091145		Folic Acid	AIPING PHARMACEUTICAL INC	TABLET	CDER/OGD	Approved	07/12/2013	
ANDA-040756		Folic Acid Tablets	PH HEALTH LTD	TABLET	CDER/OGD	Approved	06/04/2010	
ANDA-090035		Folic Acid	CHARTWELL MOLECULAR HOLDINGS	TABLET	CDER/OGD	Approved	06/09/2009	
ANDA-040796		Folic Acid	LEADING PHARMA LLC	TABLET	CDER/OGD	Approved	01/12/2009	
ANDA-040625		Folic Acid	AMNEAL PHARMACEUTICALS	TABLET	CDER/OGD	Approved	07/21/2005	
ANDA-040582		Folic Acid	SUN PHARMACEUTICAL INDUSTRIES	TABLET	CDER/OGD	Approved	07/18/2005	
ANDA-040514		Folic Acid	JUBILANT CADISTA PHARMACEUTICAL	TABLET	CDER/OGD	Approved	06/14/2005	
ANDA-089202		Folic Acid	FRESENIUS KABI USA LLC	INJECTION	CDER/OGD	Approved	02/18/1986	
ANDA-084158		Folic Acid	PHARMERAL INC	TABLET	CDER/OGD	Approved	05/08/1974	
ANDA-080816		Folic Acid	LANNETT CO INC	TABLET	CDER/OGD	Approved	05/06/1974	
ANDA-080600		Folic Acid	HIKVA INTERNATIONAL PHARMACE	TABLET	CDER/OGD	Approved	03/31/1972	
ANDA-080690		Folic Acid	WATSON LABORATORIES	TABLET	CDER/OGD	Approved	12/23/1971	
NDA-005897		Folvite (Folic Acid)	WYETH PHARMACEUTICALS INC	MISCELLANEOUS	CDER/OND/OCHEN/DGE	Approved	06/05/1947	
NDA-216395	Unknown	Quorlic (folic acid) oral solution, 1 mg/5 mL	CMP DEVELOPMENT LLC	SOLUTION	CDER/OND/OCHEN/DNH	Pending	03/26/2025	Treatment of megaloblastic anemias due to a deficiency of folic acid, as may be seen in tropical or nontropical sprue. Treatment of anemias of nutritional origin, pregnancy, infancy, or childhood. It is effective in treatment of megaloblastic anemias due to a deficiency of folic acid (as may be seen in tropical or non tropical sprue) and in anemias of nutritional origin, pregnancy, infancy or childhood
IND-144328	Commercial	Folic Acid	CMP DEVELOPMENT LLC		CDER/OND/OCHEN/DNH	Presubmission	06/21/2019	Unknown, treatment of megaloblastic anemias due to deficiency of folic acid (as may be seen in tropical or nontropical sprue) and in anemias of nutritional origin, pregnancy, infancy or childhood

Source: DARRTS Search August 2025

Folic Acid (API): Summary Nonclinical Information

- Relevant [Toxicity from PubChem \(link\)](#)

Table 3. Folic Acid Toxicology-LD₅₀

Species	Route	LD ₅₀ (mg/kg)	HED		Reference
			Based in BSA (mg/kg)	60 Kg adult (mg)	
Rat	intravenous	500	80.65	4839.0	Drugs in Japan, -(1409), 1995
Mouse	oral	10000	813.01	48780.6	Toxicology and Applied Pharmacology., 23(537), 1972 [PMID:4674811]
Mouse	intraperitoneal	85	6.91	414.6	Experientia., 41(72), 1985 [PMID:3967741]
Mouse	subcutaneous	LDLo 200	16.26	975.6	Proceedings of the Society for Experimental Biology and Medicine., 71(544), 1949
Mouse	intravenous	282	22.93	1375.8	Toxicology and Applied Pharmacology., 23(537), 1972 [PMID:4674811]
Rabbit	intravenous	410	132.26	7935.6	Drugs in Japan, -(1409), 1995
Guinea Pig	intravenous	120	26.09	1565.4	Drugs in Japan, -(1409), 1995

BSA= Body-Surface-Area; HED= Human Equivalent Dose ; LD₅₀= median lethal dose; LDLo= lethal dose low
Source: PubChem Search - August 2025

Master File (b) (4) Flavors

(b) (4) eCTD DMF# (b) (4) -:

Information files:

- [Mixed Berry Flavor \(b\) \(4\)](#) Ingredients
- [Certification of Analysis](#)
- [3.2.P.4.4 Justification of Specifications Mix Berry Flavor](#)
- [3.2.P.4.4 Regulatory Specification for Mixed Berry Flavor, \(b\) \(4\)](#)
- [3.2.P.4.4 Safety Data Sheet for Mixed Berry Flavor, \(b\) \(4\)](#)

US CFR reference Categories for listed ingredients are detailed in Table 4. Individual ingredient information is detailed in Table 5.

Table 4. US CFR Reference

Title 21- Chapter I - Subchapter B-	US CFR Reference	Category	Explanation
Part 172 Subpart F	172.515	Synthetic flavoring substances and adjuvants.	Synthetic flavoring substances and adjuvants may be safely used in food in accordance with the following conditions. (a) They are used in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice.

				(b) They consist of one or more of the following, used alone or in combination with flavoring substances and adjuvants generally recognized as safe in food, prior-sanctioned for such use, or regulated by an appropriate section in this part

(b) (4)



Table 5. Composition of Mixed Berry Flavor (b) (4): Pharm/Tox Data

Component	Name Listed in Title 21 (link)	US CFR Reference	CAS Number	IID limit from FDA Database oral solution /suspension	Quantity per MDD (µg)	Data LD50 or NOAEL oral route	HED based on BSA	FDA GRAS/EU-ADI or reference EIH	Links to eCFR :: 21 CFR 172.515 -- Synthetic flavoring substances and adjuvants.
(b) (4)									

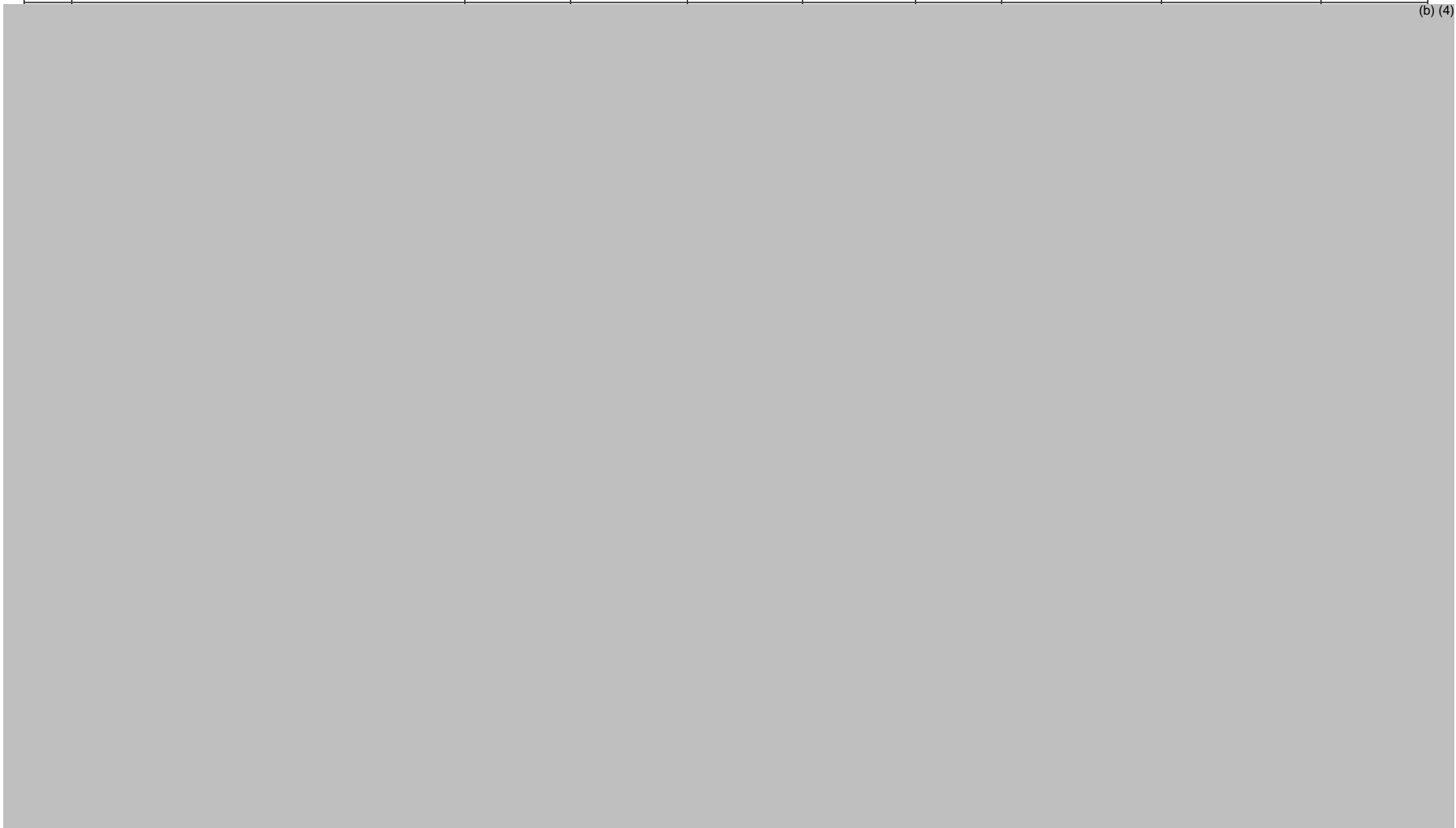
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Potential Impurities in Drug Substance and Drug Product are described in Table 6.

Table 6. Evaluation of Potential Impurities in Drug Substance and Drug Product

	IUPAC Chemical Name	CAS#	Process/ Degradation Impurity	Source /Mechanism	Acceptance Criteria	Quantity per MDD at 1 mg (µg)	Q3A (R2) Threshold /Action	Q3B (R2) Threshold /Action	(Q)SAR Report Mutagenic Potential*

(b) (4)



Computational Toxicology Consult: (Q)SAR Report

To: Vanesa Sanchez (CDER/OND/OCHEN/DPTCHEN)
cc: Bo Lee (CDER/OND/OCHEN/DPTCHEN)
From: Benon Mugabe and Naomi Kruhlak (CDER/OTS/OCP/DARS: Computational Toxicology Consultation Service)
Re: NDA 216395 – ICH M7 Bacterial Mutagenicity (Q)SAR Analysis for Folic acid Impurities
Date: September 3, 2025

Summary

Four impurities from NDA 216395 were submitted to the CDER/OTS/OCP/DARS Computational Toxicology Consultation Service (CTCS) for bacterial mutagenicity assessment using (Q)SAR models. A (Q)SAR analysis was performed by the applicant to classify the impurities for mutagenic potential under the ICH M7(R2) guideline for the drug substance Folic acid (API). The ICH M7(R2) guideline recommends the use of both a statistical-based and an expert rule-based methodology for a complete (Q)SAR analysis. The applicant performed a bacterial mutagenicity assessment using the statistical-based model Sarah Nexus 3.3.0 and the expert rule-based model Derek Nexus 6.3.0 for one of the impurities, **Compound 1**. No (Q)SAR data from the applicant were found for the remaining impurities. The statistical- based and expert rule-based systems Sarah Nexus and Derek Nexus are complementary methodologies and are acceptable to the agency. However, CTCS was consulted to confirm that the applicant's (Q)SAR assessment adequately characterizes the mutagenic potential of **Compound 1** and to provide in-house predictions for **Compounds 2 - 4**.

To confirm the applicant's conclusions, the four impurities were evaluated by CTCS for bacterial mutagenicity using three (Q)SAR models: Derek Nexus 6.4.2 (DX), Leadscope Model Applier 2025.0.1-3 Bacterial Mut v2 model (LMA), and CASE Ultra 1.9.2.4 GT1_BMUT model 1.9.2.0 (CU). These are the most recent versions of the models. All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusions. The (Q)SAR assessment of mutagenic potential for the compound(s) is consistent with recommendations described in the ICH M7(R2) guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). The following table summarizes the overall predictions from the applicant and the agency for each compound.

No.	Chemical Name	Applicant's Bacterial Mutagenicity Overall Prediction ¹	Agency's Bacterial Mutagenicity Expert Prediction ¹
1	Compound 1	-	-
2	Compound 2	N/A	-
3	Compound 3	N/A	-
4	Compound 4	N/A	-

- = negative; N/A = no prediction available.

No.	Chemical Name	Structure	Bacterial Mutagenicity Predictions ²				Comments
			DX	LMA	CU	Overall Expert	
1	Compound 1	(b) (4)	-	-	-	-	Compound 1 is predicted to be negative for bacterial mutagenicity.
2	Compound 2	(b) (4)	-	-	-	-	Compound 2 is predicted to be negative for bacterial mutagenicity.
3	Compound 3	(b) (4)	-	-	-	-	Compound 3 is predicted to be negative for bacterial mutagenicity.
4	Compound 4	(b) (4)	-	-	-	-	Compound 4 is predicted to be negative for bacterial mutagenicity.

- = negative.

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/

VANESA C SANCHEZ
01/13/2026 10:44:00 AM

BO YEON Y LEE
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