CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216395Orig1s000

OTHER REVIEW(S)

Division of Nonmalignant Hematology
Associate Director for Labeling Review of the Prescribing Information

Product Title	**QUIOFIC® (folic acid) oral solution**
Applicant	CMP Development
Application/Supplement Number	NDA 216395
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Approved Indication(s)	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
Date FDA Received Application	3/26/2025
Review Classification (Priority/Standard)	Standard
Action Goal Date	01/26/2026
Review Date	01/06/2026
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: This application is submitted under 505(b)(2) for a folic acid solution 1mg/ 5 mL relying on FDA's previous findings of safety and efficacy for the discontinued listed drug (FOLVITE) folic acid tablets, 1 mg held by Wyeth Pharma (NDA 005897). The conducted BA/BE studies were conducted agains ANDA 040625 by AMNEAL (listed as reference standard (RS) but not the RLD). Per the Orange

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.
[3] See *PLR Requirements for PI* website for PLR labeling guidances.

Book, the RLD for folic acid tablets is ANDA 080680 by Watson Laboratories. The Applicant stated in the cover letter that the Watson Labs product was not available for comparative purposes but was not discontinued.
The IND associated with this application is 144328 originally submitted on 6/21/2019.

Regulatory Recommendation: From the labeling perspective, this application is recommended for approval with final agreed upon labeling as of 12/19/25.

Labeling Section	FDA Revision	Rationale
Highlights	Added established pharmacologic class to indications statement. Removed the pediatric age Range from the indication. Added route of administration to Dosage and Administration Section. Strength revised to mg/mL. Updated adverse reactions listing to include nausea, anorexia, and bloating and remove “allergic reactions”. Deleted the Use in Specific Population subsection.	Per PLR requirements, the EPC should be included in the indication statement in HL. The entire pediatric population is covered (per the Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling Guidance for Industry, Section IIIA). Failure to include the route of administration may lead to wrong route errors. Per USP General Chapter <7>. No rates were provided in section 6 or known. We identified the most common ARs through ex-US regulator sites. This is an optional heading that may be deleted. This section should include a concise summary of any clinically important differences in response or use of the drug in specific populations.
Indications and Usage	Revised indication from: “QUIOFIC is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid (as may be seen in tropical or nontropical sprue) and in anemias of nutritional origin, pregnancy, infancy, or Childhood” to “Quiofic is indicated for the treatment of megaloblastic anemias due to folic acid deficiency in adult and pediatric patients.	Current language is “indicated for” rather than “effective”. Summarized the conditions to “megaloblastic anemias” to update the nomenclature and simplify it. Specified “adult and pediatric” patient per the Indications and Usage Guidanc which states “age groups should be included in indications.
Dosage and Administration	We recommended the addition of a new 2.1 subsection to instruct patients caregivers to use an oral dosing syringe. Removed reference to parenteral administration. We recommended presenting the doses	Evidence suggests that use of oral syringes may decrease the risk of wror dose error, particularly when measurin smaller doses. Not relevant to the oral formulation. Presenting doses in two units of

	as a single unit of measurement (mg only). Removed reference to non-specific age groups such as "infants, children" and replaced with "pediatric patients aged to xx". . Reorganized the entire section into numbered subsections (Important Administration Information, Recommended Dosing) and separated initial dosing to maintenance dosing recommendations.	measurement (mg and mL) may cause confusion and result in wrong dose errors. For clarity. For clarity.
Dosage Forms and Strengths	Revised strength from 1 mg/5 mL to 0.2 mg/mL.	For clarity.
Contraindications	Revised from "in patients who have shown previous intolerance to the drug" to "in patients with a history of hypersensitivity reaction to folic acid or any of the ingredients of QUIOFIC".	Strengthen the contraindication from "intolerance" to "hypersensitivity reaction" as this is more consistent with a true contraindication.
Warnings and Precautions	Updated the Warning title of 5.1 from Pernicious Anemia to Risk of Obscuring Diagnosis of Pernicious Anemia. Updated the text of the Warning.	To more accurately describe the risk. To update nomenclature and be more consistent with the W&P Guidance.
Adverse Reactions	Added the standard introductory disclaimer at the beginning of the subsection. Organized the list of adverse reactions in bulleted format with less descriptive text.	Per the Adverse Reactions Guidance. For clarity.
Drug Interactions	Removed text that described information about the condition of "folate deficiency". Revised to present by "Impact of Folic Acid on Other Drugs" and "Impact of Other Drugs on Folic Acid"	Per PLR guidance; does not reflect a DDI. Per Drug Interactions Guidance.
Use in Specific Populations	8.1, 8.2 revised to remove pregnancy category, add Risk Summary and 8.4 Pediatric Use subsection. Deleted proposed 8.3. Added 8.4 Pediatric Use.	Per PLLR Guidance and Pediatric Use Guidance. No adverse effects on male or female fertility were reported related to folic acid use. Further, the current indication is not for treatment of male infertility so the mention of the [redacted] (b) (4) is not warranted. Required per 21CFR201.57.
Overdosage	Removed all proposed text and added "Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations."	The proposed text did not describe an overdose situation. Per current practices and PLR Guidance.

Description	Revised to describe each 1 mL of solution rather than each 5 mL of solution.	Per USP Chapter >7>
Clinical Pharmacology	Revised text.	Per Clinical Pharmacology guidance.
Nonclinical Toxicology	No change.	
Clinical Studies	No section 14.	
How Supplied/Storage and Handling	Revised strength from 1 mg/5 mL to 0.2 mg/mL. Added Store and dispense in the origin container to protect from light and "discard unused portion 30 days after first opening".	Strength should be presented per mL. Must include storage conditions and describe the rationale for why it must b dispensed in a certain manner. Discard instructions added.
Patient Counseling Information	Section 17 added (was missing).	Except in rare circumstances, this section is always included.

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/s/

VIRGINIA E KWITKOWSKI
01/06/2026 12:23:14 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 20, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216395
Product Name, Dosage Form, and Strength:	Quiofic (folic acid) oral solution, 1 mg/5 mL[a]
Applicant Name:	CMP Development LLC. (CMC)
FDA Received Date:	November 19, 2025
TTT ID #:	2025-13866-4
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] During the review cycle, the strength was revised from “1 mg/5 mL” to “0.2 mg/mL”.

1 PURPOSE OF MEMORANDUM

CMP Development LLC. (CMC) submitted revised container label received on November 19, 2025 for Quiofic. We reviewed the revised container label for Quiofic (Appendix A) to determine if it is acceptable from a medication error perspective. The revision was in response to a recommendation that we made during a previous label and labeling review.[b]

2 CONCLUSION

CMP Development LLC. (CMC) implemented our recommendation and we have no additional recommendations at this time.

[b] Black, S. Review of Revised Label and Labeling for Quiofic (NDA 216395). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 NOV 04. TTT ID: 2025-13866-3.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON NOVEMBER 19, 2025

Container Label:

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/s/

SUE L BLACK
11/20/2025 01:49:29 PM

NICOLE F IVERSON
11/21/2025 11:04:49 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 4, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216395
Product Name, Dosage Form, and Strength:	Quiofic (folic acid) oral solution, 0.2 mg/mL[a]
Applicant Name:	CMP Development LLC. (CMC)
FDA Received Date:	October 23, 2025
TTT ID #:	2025-13866-3
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] During the review cycle, the strength was revised from “1 mg/5 mL” to “0.2 mg/mL”.

1 PURPOSE OF MEMORANDUM

CMP Development LLC. (CMC) submitted revised container label received on October 23, 2025 for Quiofic. We reviewed the revised container label for Quiofic (Appendix A) to determine if it is acceptable from a medication error perspective. During the review cycle, the Office of Pharmaceutical Quality (OPQ) determined that the in-use stability data showed the proposed drug product is stable up to 30 days after opening the bottle. Therefore, OPQ recommended the storage information in the labels and labeling be revised to reflect discarding unused portions 30 days after first opening.

2 CONCLUSION

The container label is unacceptable from a medication error perspective. We provide the identified medication error issue, our rationale for concern, and our proposed recommendation to minimize the risk for medication error for CMP Development LLC. (CMC) in Section 3.

3 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC. (CMC)

A. Container Label

1. The Office of Pharmaceutical Quality (OPQ) has determined that the proposed product is stable up to 30 days after opening the bottle. We recommend including the discard statement and space for end-users to write the beyond-use date on the container label after the statement “Store and dispense in the original container to protect from light.”. For example:

   Discard unused portion 30 days after first opening.
   Discard after: ___/____/____

   In addition, consider changing the color of the font, surrounding this information with a box, and/or highlighting the information to draw attention to this important information.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON OCTOBER 23, 2025

Container Label:

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/s/

SUE L BLACK
11/04/2025 07:48:09 AM

NICOLE F IVERSON
11/04/2025 08:27:10 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 28, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216395
Product Name, Dosage Form, and Strength:	Quiofic (folic acid) oral solution, 0.2 mg/mL[a]
Applicant Name:	CMP Development LLC. (CMC)
FDA Received Date:	October 23, 2025
TTT ID #:	2025-13866-2
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] During the review cycle, the strength was revised from “1 mg/5 mL” to “0.2 mg/mL”.

1 PURPOSE OF MEMORANDUM

CMP Development LLC. (CMC) submitted revised container label received on October 23, 2025 for Quiofic. We reviewed the revised container label for Quiofic (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous label and labeling review.[b]

2 CONCLUSION

CMP Development LLC. (CMC) implemented our recommendation and we have no additional recommendations at this time.

[b] Black, S. Review of Revised Label and Labeling for Quiofic (NDA 216395). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 OCT 21. TTT ID: 2025-13866-1.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON OCTOBER 23, 2025

Container Label:

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/s/

SUE L BLACK
10/28/2025 11:57:52 AM

NICOLE F IVERSON
10/28/2025 02:02:39 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 21, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216395
Product Name, Dosage Form, and Strength:	Quiofic (folic acid) oral solution, 1 mg/5 mL
Applicant Name:	CMP Development LLC. (CMC)
FDA Received Date:	October 9, 2025
TTT ID #:	2025-13866-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

CMP Development LLC. (CMC) submitted revised container label received on October 9, 2025 for Quiofic. We reviewed the revised container label for Quiofic (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

CMP Development LLC. (CMC) implemented all of our recommendations. CMP confirmed that the format of the expiration date is YYYY/MMM where the month will be expressed in alphabetical characters.

The container label is unacceptable from a medication error perspective. We provide the identified medication error issue, our rationale for concern, and our proposed recommendation to minimize the risk for medication error for CMP Development LLC. (CMC) in Section 3.

3 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC. (CMC)

A. Container Label

1. The net quantity statement is in close proximity to the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing. We recommend creating more white space between the net quantity statement and the strength statement. Additionally, we recommend relocating the net quantity statement away from the product strength, such as to the bottom right or left of the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

[a] Black, S. Label and Labeling Review for Quiofic (NDA 216395). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 OCT 01. TTT ID: 2025-13866.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON OCTOBER 9, 2025

Container Label:

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SUE L BLACK
10/21/2025 07:58:26 AM

NICOLE F IVERSON
10/21/2025 09:20:58 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/17/2025

TO: Office of Bioequivalence (OB)
Office of Generic Drugs

TO: Division of Non-Malignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: (b) (4)
ANDA 218829
NDA 216395

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Inspections and Investigations (OII) conducted an inspection of the site in March 2025. The inspection was conducted under the following submission: (b) (4).

The following items were discussed with the site:

(b) (4)

After review of the inspection findings, OSIS concluded that the findings did not impact data reliability or human subject protection..

Site

Facility Type	Facility Name	Facility Address
Clinical	Synergen Bio Pvt., Ltd.	Unit No. 101 to 104 and 309 to 311, Sai Chambers, 302, Old Mumbai Pune Highway, Wakadewadi, Shivajinagar, Pune, Maharashtra, India

JAMES J. LUMALCURI -S

Digitally signed by JAMES J. LUMALCURI -S
Date: 2025.06.17 09:02:34 -04'00'

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/s/

JAMES J LUMALCURI
06/17/2025 09:20:30 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 16, 2025

To: Bijal Patel, MS, Regulatory Project Manager,
Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling,
(DNH)

From: Melissa Khashei, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for QUIOFIC® (folic acid) oral solution

NDA: 216395

Background:
In response to DNH's consult request dated April 14, 2025, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for QUIOFIC® (folic acid) oral solution.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 2, 2025, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on March 26, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

15 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MELISSA KHASHEI
10/16/2025 11:20:12 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 1, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216395
Product Name, Dosage Form, and Strength:	Quiofic (folic acid) oral solution, 1 mg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	CMP Development LLC. (CMC)
FDA Received Date:	March 26, 2025, April 7, 2025, April 21, 2025, and July 2, 2025
TTT ID #:	2025-13866
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Quiofic (folic acid) oral solution, we reviewed the proposed Quiofic Prescribing Information (PI) and container label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Quiofic (folic acid) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Folvite (folic acid), NDA 005897. The Reference Standard (RS) is folic acid tablets 1 mg by Amneal Pharmaceuticals (ANDA 040625).

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that *Summary of Container/Closure System*[a] states [(b) (4)] ” We also note that the Section 16 of the Prescribing Information states the product is supplied in an “amber” bottle and to [(b) (4)] .”. However, Section 16 does not discuss [(b) (4)] or light protection or if the product should be stored in the original container. We reached out to Office Pharmaceutical Quality (OPQ) to confirm if the product should be stored and dispensed in the original container or if any well-closed container with child-resistant closure is appropriate and if additional warnings such as protect from [(b) (4)] light are warranted. OPQ confirmed the product should be stored and dispensed in the original container, [(b) (4)] In addition, OPQ agreed with our proposal to update the storage information in the labels and labeling from [(b) (4)] .” to “Store and dispense in the original container to protect from light.”.

[a] Summary of Container/Closure System. Farmville (NC): CMP Development LLC.; 26 MAR 2025> NDA 216395. Available from: \\CDSESUB1\EVSPROD\nda216395\0001\m3\32-body-data\32p-drug-prod\folic-acid-oral-sol\32p7-cont-closure-sys\32p71-sum-cont-clos-sys\32p71-sum-cont-clos-sys.pdf.

4 CONCLUSION

The proposed Quiofic Prescribing Information (PI) and container label may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Non-Malignant Hematology (DNH) in Section 5 and for CMP Development LLC. in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. General Issues
    a. The strength is not presented as XX mg/mL. Drug products not in unit-dose packaging shall be labeled to show the quantity of each active moiety and/or drug substance in each milliliter in accordance with General Chapter <7>. Revise the strength from "1 mg/5 mL" to "0.2 mg/mL" in accordance with USP General Chapter <7>.
    b. The Dosage and Administration Section uses the less than symbol "<". The use of symbols instead of words may lead to misinterpretation and medication error. We recommend replacing the less than symbol "<" with the intended meaning "less than" in the Dosage and Administration Section.
    c. Doses in the Dosage and Administration Section are presented in two different units of measurement: mg and mL. Presenting doses in two different units of measurement may cause confusion and result in wrong dose errors. We recommend presenting the doses in a single unit of measurement (i.e., mg only).
    d. The route of administration is missing in the Dosage and Administration Section. Failure to include the route of administration may lead to wrong route errors. We recommend adding the route of administration "orally" to each recommended dosage.
2. Section 2 Dosage and Administration
    a. As currently presented, Section 2 of the PI does not contain a statement instructing patients and/or caregivers to use an oral dosing syringe to measure the prescribed dose. Evidence suggests that use of oral syringes may decrease the risk of wrong dose error, particularly when measuring smaller doses. We recommend creating a new Section 2.1 *Important Administration Information* and adding the following statement: "Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy."
3. Section 16 How Supplied/Storage and Handling
    a. As currently presented, the *How Supplied* statement contains the size of the bottle (b) (4)), which may be misinterpreted as the fill volume. We

recommend removing this information and revising to "QUIOFIC (folic acid) Oral Solution, 0.2 mg/mL is a yellow solution with a mixed berry flavor supplied in amber PET bottles with a child-resistant closure containing 75 mL of oral solution (NDC 69499-501-75)."

b. As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) do not follow the first numeric degree measurement in the temperature ranges and is inconsistent with storage information on the container label. We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges for consistency with the container label. For example, revise to "Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]."

c. As currently presented, the storage statement "(b) (4) does not indicate that the product should be dispensed and stored in the original container. In concurrence with OPQ, we recommend revising the storage information in the labels and labeling from (b) (4) " to "Store and dispense in the original container to protect from light.".

4. Section 17 Patient Counseling

a. As currently presented, Section 17 of the PI does not contain a statement instructing patients and/or caregivers to use an oral dosing syringe to measure the prescribed dose. Evidence suggests that use of oral syringes may decrease the risk of wrong dose error, particularly when measuring smaller doses. We recommend adding the following statements to Section 17: "Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy."

6 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC.

A. Container Label

1. The strength is not presented as XX mg/mL. Drug products not in unit-dose packaging shall be labeled to show the quantity of each active moiety and/or drug substance in each milliliter in accordance with General Chapter <7>. Revise the strength from "1 mg/5 mL" to "0.2 mg/mL" in accordance with USP General Chapter <7>. Along these lines, we recommend revising the statement "Each 5 mL contains: 1 mg of Folic Acid, USP" to "Each 1 mL contains: 0.2 mg of folic acid, USP".
2. As currently presented, the "Rx only" statement appears prominent, which may compete with other important information on the label. We recommend decreasing the prominence by reducing the font size for the "Rx only" statement.

3. We note that the statement "(b) (4)." is proposed on the container labels. This statement is unnecessary and contributes to label clutter. We recommend removing this statement to decrease clutter.
4. The manufacturer information (e.g., manufacturer name "Solubiomix" and (b) (4)) competes in prominence with critical product information (e.g., proprietary name, established name, strength). In addition, the (b) (4) present at the beginning of the manufacturer's name could be misinterpreted as the appearance of tablets in the bottle. Critical product information such as the proprietary name, established name, and product strength should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15. Decrease the font size of the manufacturer information or move it to the side panel so it does not compete with the prominence of important product information on the principal display panel. Additionally, we recommend deleting the (b) (4) appearing at the beginning of the manufacturer's name, Solubiomix.
5. The format for the month portion of the expiration date is unclear on the carton labeling (b) (4)). We are unable to assess the month portion of the expiration date from a safety perspective. Confusion regarding the expiration date may lead to use of expired drug product. Please clarify the format for the expiration date and whether alphabetical or numerical characters will be used to represent the month. If using alphabetical characters, then we recommend you revise the format for the month portion to three characters (for example, "JUL" versus "JU" to represent July) to prevent confusion.
6. As currently presented, the storage statement does not indicate that the product should be dispensed and stored in the original container. In concurrence with OPQ, we recommend adding the statement "Store and dispense in the original container to protect from light.".
7. As currently presented, the presentation of the established name is inconsistent with the Prescribing Information (folic acid vs. Folic Acid). For consistency with the Prescribing Information, we recommend presenting the established name as "folic acid".
8. As currently presented, the (b) (4) on net quantity statement competes in prominence with the strength statement. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). To decrease its prominence in relation to the strength statement, we recommend removing the (b) (4) on the net quantity statement.
9. As currently presented, the proprietary name is presented in all capital letters, which reduces readability. Additionally, the capital letter "I" in the name could be misinterpreted as a lower-case "l". Consider revising the proprietary name to title case (i.e., Quiofic) to improve readability and reduce the risk of misinterpretation.

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APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Quiofic received on April 21, 2025 from CMP Development LLC., and the Reference Standard (RS).

Table 2. Relevant Product Information for Quiofic and the Reference Standard (RS)		
Product Name	Quiofic	Folic acid [b] (ANDA 040625)
Initial Approval Date	N/A	07/21/2005
Active Ingredient	folic acid	folic acid
Indication	Treatment of megaloblastic anemias due to a deficiency of folic acid (as may be seen in tropical or nontropical sprue) and in anemias of nutritional origin, pregnancy, infancy, or childhood.	Treatment of megaloblastic anemias due to a deficiency of folic acid (as may be seen in tropical or nontropical sprue) and in anemias of nutritional origin, pregnancy, infancy, or childhood
Dosage Form	oral solution	tablets
Strength	1 mg/5 mL	1 mg
Route of Administration	oral	oral

[b] DailyMed. U.S. National Library of Medicine. OCT 2024. [Cited 2025 JUN 25]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c8fe09f0-b32b-43e3-8de7-ed38593b33b4.

Table 2. Relevant Product Information for Quiofic and the Reference Standard (RS)		
Product Name	Quiofic	Folic acid [b] (ANDA 040625)
Dose and Frequency	Doses greater than 0.1 mg (0.5 mL) should not be used unless anemia due to vitamin B12 deficiency has been ruled out or is being adequately treated with a cobalamin. Daily doses greater than 1 mg (0.5 mL) do not enhance the hematologic effect, and most of the excess is excreted unchanged in the urine. The usual therapeutic dosage in adults and children (regardless of age) is up to 1 mg (5 mL) daily. Resistant cases may require larger doses. When clinical symptoms have subsided and the blood picture has become normal, a daily maintenance level should be used as follows: • Infants: 0.1 mg (0.5 mL) daily • Children <4 years: up to 0.3 mg (1.5 mL) daily • Adults and Children 4 years and older: 0.4 mg (2 mL) daily • Pregnant and Lactating Women: 0.8 mg (4 mL) daily; but never less than 0.1 mg (0.5 mL) per day Patients should be kept under close supervision and adjustment of the maintenance level made if relapse appears imminent.	Oral administration is preferred. Although most patients with malabsorption cannot absorb food folates, they are able to absorb folic acid given orally. Parenteral administration is not advocated but may be necessary in some individuals (e.g., patients receiving parenteral or enteral alimentation). Doses greater than 0.1 mg should not be used unless anemia due to vitamin B deficiency has been ruled out or is being adequately treated with a cobalamin. Daily doses greater than 1 mg do not enhance the hematologic effect, and most of the excess is excreted unchanged in the urine. The usual therapeutic dosage in adults and children (regard less of age) is up to 1 mg daily. Resistant cases may require larger doses. When clinical symptoms have subsided and the blood picture has become normal, a daily maintenance level should be used, i.e., 0.1 mg for infants and up to 0.3 mg for children under 4 years of age, 0.4 mg for adults and children 4 or more years of age, and 0.8 mg for pregnant and lactating women, but never less than

Table 2. Relevant Product Information for Quiofic and the Reference Standard (RS)		
Product Name	Quiofic	Folic acid [b] (ANDA 040625)
	In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased.	0.1 mg/day. Patients should be kept under close supervision and adjustment of the maintenance level made if relapse appears imminent. In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased.
How Supplied	QUIOFIC (folic acid) Oral Solution, 1 mg/5 mL is a yellow solution with a mixed berry flavor supplied in (b) (4) amber PET bottles with a child-resistant closure containing 75 mL. NDC 69499-501-75	Folic Acid Tablets USP, 1 mg, are supplied as round, yellow tablets imprinted “AN” and “361” on one side and scored on the other side. They are available as follows: Bottles of 10: NDC 65162-361-01 Bottles of 100: NDC 65162-361-10 Bottles of 500: NDC 65162-361-50 Bottles of 1000: NDC 65162-361-11
Storage	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. (b) (4)	Dispense in well-closed container with child-resistant closure. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Container Closure	Folic Acid Oral Solution, 1 mg/5 mL is packaged in (b) (4), Amber, PETE Bottles with (b) (4) Child Resistant Caps	Not provided

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APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Quiofic labels and labeling submitted by CMP Development LLC.

- Prescribing Information received on July 2, 2025, available from \\CDSESUB1\EVSPROD\nda216395\0008\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-pi-track.docx
- Container label received on March 26, 2025

B.2 Container Label Images

Container Label:

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On June 9, 2025, we searched for previous DMEPA reviews relevant to this current review using the term, “folic acid”. Our search identified no previous reviews.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: October 1, 2025 **Date consulted:** May 12, 2025

From: Kevin Clark, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, Division Director, DPMH

To: Division of Non-Malignant Hematology (DNH)

Drug: Quiofic (folic acid) Oral Solution, 1 mg/5 mL

NDA: 216395

Applicant: CMP Development, LLC

Subject: Pregnancy and Lactation Labeling

Indication: 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.

Materials Reviewed:

- March 26, 2005, Applicant's NDA submission
- May 12, 2025, consult request from DNH to DPMH-Maternal Health
- July 2, 2025 (SDN 8), Applicant's response to information request

- October 19, 2020, DPMH Review of NDA 021625 S-024, MVI (multiple vitamins injection) for intravenous use, DARRTS Reference ID: 4687516[1]

Consult Question: "Received a New NDA indicated for the 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… This indication targets the patient population from infancy, childhood and pregnant women."

INTRODUCTION AND BACKGROUND

On March 26, 2025, the Applicant, CMP Development LLC, submitted a New Drug Application (NDA) for Quiofic (folic acid) Oral Solution, 1 mg/5 mL to the Division of Non-Malignant Hematology (DNH) under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. DNH consulted the Division of Pediatrics and Maternal Health (DPMH) on May 12, 2025 to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- The product was developed under IND 144328.
- For this 505(b)(2) NDA, the Applicant proposes to rely on the FDA's findings of safety and effectiveness for the Listed Drug (LD), Folvite (folic acid) tablets, 1 mg (NDA 005897, approved 6/5/1947). This product is discontinued, but not for reasons of safety or effectiveness (per Orange Book, accessed 8/1/2025). For labeling, the Applicant proposes to rely on the Reference Standard (RS), Folic Acid tablets, 1 mg (ANDA 040625, approved 7/21/2005).
- DPMH-Maternal Health has not conducted any previous reviews of folic acid products as monotherapy. However, DPMH-Maternal Health has completed the following reviews of multivitamin products containing folic acid:
    - October 19, 2020, DPMH Review of NDA 021625 S-024, MVI Adult for intravenous use, Kristie Baisden, DO, DARRTS Reference ID: 4687516[1]
    - September 19, 2024, DPMH review of Prior Approval labeling Supplements for NDA 021265 and 021163, Infuvite Adult and Infuvite Pediatric, for intravenous use, Carrie Ceresa, Pharm D., MPH, DARRTS Reference ID: 5447917[1]

Current State of the Labeling

- Labeling for the RS is not in Physician's Labeling Rule (PLR) nor Pregnancy and Lactation Labeling Rule (PLLR) format. Labeling for the LD is no longer available as the product has been discontinued.
- Labeling for the RS carries no contraindication, warning, or precaution regarding pregnancy and lactation, nor recommendation for pregnancy testing.
- Labeling carries the following in the Pregnancy and Nursing Mothers subsections:

    Pregnancy
    Teratogenic Effects
    Pregnancy Category A

[1] The DPMH review of MVI was part of the materials reviewed for this consult but were not a source relied upon for the labeling recommendations below.

Folic acid is usually indicated in the treatment of megaloblastic anemias of pregnancy. Folic acid requirements are markedly increased during pregnancy, and deficiency will result in fetal damage (see **INDICATIONS AND USAGE**).

Studies in pregnant women have not shown that folic acid increases the risk of fetal abnormalities if administered during pregnancy. If the drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, folic acid should be used during pregnancy only if clearly needed.

Nursing Mothers
Folic acid is excreted in the milk of lactating mothers. During lactation, folic acid requirements are markedly increased; however, amounts present in human milk are adequate to fulfill infant requirements, although supplementation may be needed in low-birth-weight infants, in those who are breast-fed by mothers with folic acid deficiency (50 mcg daily), or in those with infections or prolonged diarrhea.

- Serious adverse reactions listed in labeling include rare allergic reactions and anaphylaxis.
- Other adverse reactions include gastrointestinal events, including anorexia, nausea, abdominal distention, flatulence, and a bitter or bad taste, have been reported in patients receiving 15 mg folic acid daily (15 times the maximum proposed daily dose) for 1 month. Other adverse reactions reported in patients receiving 15 mg daily include altered sleep pattern, difficulty in concentrating, irritability, overactivity, excitement, mental depression, confusion, and impaired judgment.
- The Drug Interactions section of labeling for the RS does not list any interaction with oral contraceptives.
- Labeling for the RS carries no nonclinical data.

REVIEW
PREGNANCY
Megaloblastic Anemia and Pregnancy
It is estimated that 30 percent of reproductive age females are anemic. Among pregnant women, the prevalence is even higher. The World Health Organization (WHO) estimates that over 40 percent of pregnancies are complicated by anemia. Variations in regional and global prevalence of anemia during pregnancy reflect socioeconomic status and associated nutritional deficiencies.[2] The majority of anemia in reproductive age females is due to low or absent iron stores, contributing to more than 50 percent of anemia in pregnancy worldwide.[3] Anemia during pregnancy can adversely affect both the mother and the fetus. Severely anemic pregnant

[2] Auerbach M, Landy H, Anemia in pregnancy, UpToDate.com, last updated 4/23/2025, accessed 8/7/2025
[3] Amarasinghe GS, Agampodi TC, Mendis V, Malawanage K, Kappagoda C, Agampodi SB. Prevalence and aetiologies of anaemia among first trimester pregnant women in Sri Lanka; the need for revisiting the current control strategies. BMC Pregnancy Childbirth. 2022 Jan 6;22(1):16. doi: 10.1186/s12884-021-04341-z. PMID: 34986796; PMCID: PMC8734253.

women have a 2.36 times higher risk of death than other pregnant women and are more vulnerable to adverse pregnancy outcomes. Maternal anemia also increases the baby's risk for neurodevelopmental problems, obesity, cardiac diseases, and anemia.[4]

Megaloblastic anemia may result from deficiencies in folic acid/folate or vitamin B12. Folate is the natural form found in food, while folic acid is the synthetic form used in supplements or fortified foods. Folate deficiency is the most common cause of megaloblastic anemia during pregnancy and is often associated with diets low in animal proteins, fresh leafy vegetables, and legumes.[3] This review will focus on megaloblastic anemia caused by folic acid/folate deficiency. Pregnant women are especially vulnerable to folate deficiency as its requirement is significantly increased in pregnancy. Folate is essential for purine and thymidine nucleotide biosynthesis and homocysteine metabolism. Therefore, folate deficiency leads to DNA synthesis abnormalities, homocysteine elevation, and altered cellular gene expression. Inhibited DNA synthesis affects mitosis, causing ineffective erythropoiesis from hematopoietic precursor cells. Macrocytic anemia, pancytopenia and hyper-segmented neutrophils may become evident in the blood. Reduction of red cell lifespan is another contributor to anemia seen in folate deficiency. The same mechanisms can lead to increased risk for congenital abnormalities (such as neural tube defects), fetal growth retardation, preterm delivery, and neonatal folic acid deficiency in addition to maternal anemia.[4]

Nonclinical Experience

Labeling for the RS contains no nonclinical toxicology information, and the Applicant did not conduct reproductive toxicology studies with folic acid during their development program. As such, the Applicant is relying on published literature to support the nonclinical safety of folic acid, including reproductive toxicology. Information from published literature cited by the Applicant regarding reproductive toxicology included the following findings. Folic acid in small doses (5 mg/kg/day) reverses developmental toxicity in pups of female pregnant rats. However, high maternal folic acid levels are associated with changes in body weight, metabolism, increased risk for mammary adenocarcinomas, and gene expression in the cerebellum in rat offsprings. In mice, disrupted fetal development, embryonic loss, and embryonic developmental delay can be caused by high-dose folic acid supplementation in maternal food during gestation. Refer to the Applicant's Toxicology Written Summary (Module 2.6.6 of the NDA submission) and the Pharmacology/Toxicology review by Vanesa Sanchez, PhD and Bo Lee, PhD.

Review of Pharmacovigilance Database

The Applicant's NDA submission does not specifically state whether or not their product is currently approved in any jurisdiction. Pregnant females were excluded from the comparative BA studies conducted by the Applicant. No pregnancies were reported during the development program.

Review of Literature

Applicant's Review of Literature

The Applicant's review of literature identified 3 publications related to the effects of folic acid use during pregnancy. A brief summary of these publications is presented below.

A publication by Rolschau, et. al. (1999)[4] reported results of a randomized, double-blind trial to evaluate the efficacy of folic acid tablets 1 mg and 2.5 mg during pregnancy. All women of childbearing age living on the island of Funen, Denmark (population 500 000) were offered a supplement of folic acid over a period of 3 years and 3 months. A total of 8184 women were evaluated. No adverse effects were reported. The study concluded that 1.0 mg folic acid had the same effect as 2.5 mg. The effects of supplementing the diet with folic acid given preconceptionally or in the first half of pregnancy were a slight increase of birth weight and a decrease in the incidence of preterm labor, infants with low birth weight and small for gestational age compared with women who did not receive folic acid. The greatest effect was seen in the groups receiving folic acid preconceptionally.

A publication by Pritchard, et. al (1969)[5] reported results of a treatment trial conducted in 16 pregnant women with megaloblastic anemia hospitalized on the obstetric service at Parkland Memorial Hospital in Dallas, Texas. No adverse effects were reported. Two subjects who received a low folate diet and two who received a regular hospital diet without folic acid supplementation showed no hematologic response during an observation period of 10 days to 2 weeks. All subsequently responded well after administration of folic acid. All subjects treated with 1 mg folic acid achieved satisfactory hematologic response. The study concluded that daily supplementation with 1 mg of folic acid during pregnancy should protect all pregnant women against folate deficiency including those with multiple fetuses, chronic hemolysis, and repetitive megaloblastic anemia.

A publication by Berger, et.al (2005)[6] reported a community-based study conducted in Vietnam. A total of 732 nulliparous women who were planning to become pregnant were enrolled. The subjects received weekly doses of iron 60 mg and folic acid 3.5 mg before pregnancy, followed by weekly doses of iron 120 mg and folic acid 3.5 mg during pregnancy. This treatment program was compared to the usual practice in Vietnam of giving daily iron 60 mg-folic acid 0.25 mg tablets beginning at the first prenatal visit. The study results demonstrated that weekly supplementation before and during pregnancy improved iron and hemoglobin status in women. The prevalence of anemia and iron deficiency decreased significantly. Fewer cases of low birth weight were observed in the weekly supplementation group compared to the daily supplementation group. The study demonstrated that preventive weekly iron-folic acid supplementation was effective in controlling anemia and iron deficiency in women before and during pregnancy. The publication did not provide any information regarding adverse effects of folic acid during pregnancy.

[4] Rolschau J, Kristoffersen K, Ulrich M, Grinsted P, Schaumburg E, Foged N. The influence of folic acid supplement on the outcome of pregnancies in the county of Funen in Denmark Part I. European Journal of Obstetrics & Gynecology and Reproductive Biology 87 (1999) 105–110. PMID: 10597955

[5] Pritchard JA, Scott DE, Whalley PJ. Folic Acid Requirements in Pregnancy- Induced Megaloblastic Anemia. JAMA. 1969 May 19;208(7):1163-7. PMID: 5818714

[6] Berger J. et.al. (2005). Community Mobilization and Social Marketing to Promote Weekly Iron-Folic Acid Supplementation in Women of Reproductive Age in Vietnam: Impact on Anemia and Iron Status. Nutrition Reviews, 63(12), S95–S108.

DPMH Review of Literature

DPMH conducted a search of published literature in PubMed, Embase, and Briggs' *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk*[7] using the search terms "Folic acid" and "pregnancy", "safety events and pregnancy", "adverse effects AND pregnancy", "pregnancy outcomes", "adverse pregnancy outcomes", "congenital anomalies", "congenital defects", "pregnant women", "pregnancy AND birth defects", "pregnancy AND congenital malformations", "pregnancy AND stillbirth", "pregnancy AND miscarriage", "spontaneous abortion", "prematurity", "low birth weight", "fetal loss", "pregnancy loss", and "teratogenicity".

The DPMH review of literature was conducted with assistance from Elsa[8] to assist in the review some of the cited publications for relevant content. The content identified by Elsa and selected for inclusion in this review have been thoroughly reviewed and verified by this reviewer.

The United States Preventive Services Task Force (USPSTF) recommends that women who are capable of or planning pregnancy take a daily supplement containing 0.4 to 0.8 mg folic acid at least 1 month before conception and continuing through the first 2 to 3 months of pregnancy to reduce the risk of neural tube defects in the developing fetus.[9] The World Health Organization (WHO) recommends daily oral supplementation with 30-60 mg of iron and 0.4 mg of folic acid for pregnant women to prevent maternal anemia, puerperal sepsis, low birth weight, and preterm birth.[10]

Briggs' *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk* provides an extensive summary regarding folic acid and pregnancy, focusing on the effects of folic acid deficiency. Briggs' provides the following pregnancy summary:

> "Folic acid deficiency during pregnancy is a common problem in undernourished women and in women not receiving supplements. The relationship between folic acid levels and various maternal or fetal complications is complex. Evidence has accumulated that interference with folic acid metabolism or folate deficiency induced by drugs such as anticonvulsants and some antineoplastics early in pregnancy results in congenital anomalies. Moreover, a substantial body of evidence is now available that non-drug-induced folic acid deficiency, or abnormal folate metabolism, is related to the occurrence of birth defects and some neural tube defects (NTDs). Lack of the vitamin or its metabolites may also be responsible for some cases of spontaneous abortion and intrauterine growth restriction. For other complications, it is probable that a number of factors, of

[7] Briggs GG, Towers CV, Forinash AB. Briggs *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk.* 12th edition. [Philadelphia, PA., Lippincott Williams and Wilkins, 2022], accessed online 7/31/2025

[8] Elsa is an FDA internal, generative, artificial intelligence platform designed to assist CDER staff in review work.

[9] Viswanathan M, Urrutia RP, Hudson KN, Middleton JC, Kahwati LC. Folic Acid Supplementation to Prevent Neural Tube Defects: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2023 Aug 1;330(5):460-466. doi: 10.1001/jama.2023.9864. PMID: 37526714.

[10] Doganis D, Katsimpris A, Panagopoulou P, Bouka P, Bouka E, Moschovi M, Polychronopoulou S, Papakonstantinou E, Tragiannidis A, Katzilakis N, Dana H, Antoniadi K, Stefanaki K, Strantzia K, Dessypris N, Schüz J, Petridou ET. Maternal lifestyle characteristics and Wilms tumor risk in the offspring: A systematic review and meta-analysis. Cancer Epidemiol. 2020 Aug;67:101769. doi: 10.1016/j.canep.2020.101769. Epub 2020 Jul 10. PMID: 32659726.

> which folic acid deficiency may be one, contribute to poor pregnancy outcome. To ensure good maternal and fetal health, all pregnant women should receive sufficient dietary or supplementary folic acid to maintain normal maternal folate levels."

In addition to the well-known association for folate deficiency and neural tube defects, Briggs' also notes that several publications have proposed a possible relationship between maternal folic acid deficiency and placental abruption. However, Briggs' also notes that other case series have found no correlation. The publications referenced in Briggs' date back to the 1960s, and an attempt by this reviewer to acquire copies of the publications was not successful. Briggs' also notes conflicting reports regarding a potential association between maternal folate deficiency and low birth weight, with some sources noting a strong association and other sources noting no association. Furthermore, Briggs' notes that some anticonvulsants (e.g., phenytoin and phenobarbital) may induce maternal folic acid deficiency. It is recommended that women treated with anticonvulsants receive sufficient dietary folate or folic acid supplementation to maintain normal levels of folic acid in serum and red blood cells.

The majority of published literature regarding folic acid and pregnancy describe the risks of folic acid deficiency as described above. However, some publications mention risks associated with excess folic acid intake, i.e., greater than the recommended daily intake which was presented above. A review article by Ledowsky, et.al., (2022) reported that 25-100% of pregnant women in countries with mandatory fortification exceed the 1 mg/day upper tolerable limit, with 97% having detectable unmetabolized folic acid.[11] Another publication reported that high-dose supplementation (>1 mg/day) was associated with decreased birth length and increased low birth weight risk in a Spanish cohort. This publication also reported that doses exceeding the upper limit of 1 mg/day during periconceptional phase linked to impaired neurocognitive development, while WHO-recommended levels showed benefits. Additionally, high-dose supplementation (>5 mg/day) was associated with poor psychomotor development.[12] Another publication reported and attention problems in male children when maternal intake exceeded 10 mg/day.[13] The data regarding neurocognitive and attention problems in children of mothers who took high doses of folate before and during pregnancy were from prospective cohort studies conducted in Spain. The source publications did not provide a reason for maternal intake of doses exceeding standard recommendations.

Reviewer's Comment:
The Applicant's review was adequate. The potential risks associated with folic acid intake that exceeds current recommendations are not relevant to this product, because the indicated population includes patients with megaloblastic anemia due to folic acid/folate deficiency.

[11] Ledowsky C, Mahimbo A, Scarf V, Steel A. Women Taking a Folic Acid Supplement in Countries with Mandatory Food Fortification Programs May Be Exceeding the Upper Tolerable Limit of Folic Acid: A Systematic Review. Nutrients. 2022 Jun 29;14(13):2715. doi: 10.3390/nu14132715. PMID: 35807899; PMCID: PMC9268323.
[12] Fardous AM, Heydari AR. Uncovering the Hidden Dangers and Molecular Mechanisms of Excess Folate: A Narrative Review. Nutrients. 2023 Nov 6;15(21):4699. doi: 10.3390/nu15214699. PMID: 37960352; PMCID: PMC10648405.
[13] King A, Gerard EE. Contraception, fecundity, and pregnancy in women with epilepsy: an update on recent literature. Curr Opin Neurol. 2022 Apr 1;35(2):161-168. doi: 10.1097/WCO.0000000000001039. PMID: 35191408; PMCID: PMC9230745.

LACTATION

Nonclinical Experience

Labeling for the RS contains no nonclinical toxicology information. As such, the Applicant is relying on published literature to support the nonclinical safety of folic acid, including safety during lactation. Refer to the Applicant's Response to Information Request dated July 2, 2025 (SDN 8) for a table of animal studies related to folic acid and lactation. Additionally, refer to the Pharmacology/Toxicology review by Vanesa Sanchez, PhD and Bo Lee, PhD.

Review of Pharmacovigilance Database

The Applicant's NDA submission does not specifically state whether or not their product is currently approved in any jurisdiction. Lactating females were excluded from the comparative BA studies.

Review of Literature

Applicant's Review of Literature

In response to an Information Request, the Applicant conducted a search of the published literature regarding folic acid use in lactating women. The Applicant did not provide the search terms used in their review of literature. The search yielded 34 publications. Refer to the Applicant's Response to Information Request dated July 2, 2025 (SDN 8) for a tabular listing which included a brief summary of each of these publications, along with a list of references. Key points from the Applicant's review of literature are summarized below.

Folate concentrations in breastmilk increase as lactation progresses, with colostrum having lower levels than mature milk.[14] Folate concentrations in human milk remain relatively stable even when maternal folate status is compromised, indicating a biological priority system that protects infant nutrition at the expense of maternal stores.[15,16,17] Women taking folic acid supplements show increased unmetabolized folic acid (UMFA) levels in breast milk, with doses greater than 0.4 mg/day leading to higher concentrations of UMFA concentrations in breastmilk.[18,19] Although UMFA is present in infant plasma and feces, its metabolism and clearance, as well as its health implications in infants are not well understood.[20] Some studies suggest potential associations with food allergies and autism spectrum disorders, but findings are inconsistent and

[14] Ramasastri BV, Nutrition Research Laboratories. Folate activity in human milk. Br. J. Nutr. (1965), 19 (4):581-6. doi: 10.1079/bjn19650052.

[15] Matoth Y, Pinkas A and Sroka C. Studies on Folic acid in infancy- III. Folates in breast fed infants and their mothers. Am J Clin Nutr 1965 Apr;16(4):356-9. doi: 10.1093/ajcn/16.4.356.

[16] O'Connor DL, Green T and Picciano MF. Maternal folate status and lactation. J Mammary Gland Biol Neoplasia. 1997 Jul;2(3):279-89. doi: 10.1023/a:1026388522182.

[17] Allen LH. B Vitamins in Breast Milk: Relative Importance of Maternal Status and Intake, and Effects on Infant Status and Function. Adv Nutr. 2012 May 1;3(3):362-9. doi: 10.3945/an.111.001172.

[18] West AA, Yan J, Perry CA, Jiang X, Malysheva OV and Caudill MA. Folate-status response to a controlled folate intake in nonpregnant, pregnant, and lactating women. Am J Clin Nutr. 2012 Oct;96(4):789-800.

[19] Page R, Robichaud A, Arbuckle TE, Fraser WD, & MacFarlane AJ. (2017). Total folate and unmetabolized folic acid in the breast milk of a cross-section of Canadian women. The American Journal of Clinical Nutrition, 105, 1101–1109. doi: 10.3945/ajcn.116.137968.

[20] Cochrane KM, Elango R, Devlin AM, Hutcheon JA and Karakochuk CD. Human milk unmetabolized folic acid is increased following supplementation with synthetic folic acid as compared to (6S)-5-methyltetrahydrofolic acid. Sci Rep.2023 Jul 12;13(1):11298.

require further research.[21,22,23] Extended lactation without supplementation leads to declining maternal blood folate levels and can result in folate-deficient megaloblastic anemia, particularly in regions with poor dietary folate intake.[18,24,25]

Based on their review of literature, in their Response to Information Request, the Applicant submitted draft labeling with revisions to subsection 8.2 Lactation. Refer to the DPMH labeling recommendations below.

Review of literature submitted by the Applicant was conducted with assistance from Elsa to assist in the review each cited publication for relevant content. The content selected for inclusion in this review has been thoroughly reviewed and verified by this reviewer.

DPMH Review of Literature
DPMH conducted a search of published literature in PubMed, Embase, and Briggs' *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk* and Hale's *Medications and Mother's Milk*[26] using the search terms "Folic acid" and "lactation" and "breastfeeding".

Hale's *Medications and Mother's Milk* states, "Limited data-Compatible." Hale's also noted the active section of folic acid in breastmilk, even if the mother is deficient. Additionally, if the maternal diet is adequate, folic acid supplementation is generally not required. No potential adverse effects from excessive folate consumption by the infant are mentioned.

Briggs' *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk* states the same points as Hale's. Additionally, Briggs' notes that folate levels in newborns and breastfed infants are consistently higher than those in mothers and healthy adults. Briggs' also mentions the possibility of megaloblastic anemia in the mother if her dietary folate intake is not adequate, and she is not receiving folic acid supplements. The National Academy of Sciences' recommended daily allowance for folic acid during lactation is 0.280 mg/day. If the lactating woman's diet adequately supplies this amount, maternal supplementation with folic acid is not needed. Maternal supplementation with the RDA for folic acid is recommended for those patients with inadequate nutritional intake. No potential adverse effects from excessive folate consumption by the infant are mentioned.

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[21] Best KP, Green TJ, Sulistyoningrum DC, Sullivan TR, Aufreiter S, Prescott SL, Makrides M, Skubisz M, O'Connor DL and Palmer DJ. Maternal Late-Pregnancy Serum Unmetabolized Folic Acid Concentrations Are Not Associated with Infant Allergic Disease: A Prospective Cohort Study. J Nutr. 2021 Jun 1;151(6):1553-1560. doi: 10.1093/jn/nxab040.
[22] McGowan EC, Hong X, Selhub J, Paul L, Wood RA, Matsui EC, Keet CA, Wang X. Association between folate metabolites and the development of food allergy in children. J Allergy Clin Immunol Pract. 2020;8(1):132–140.
[23] Raghavan R, Selhub J, Paul L, Ji Y, Wang G, Hong X, Zuckerman B, Fallin MD, Wang X. A prospective birth cohort study on cord blood folate subtypes and risk of autism spectrum disorder. Am J Clin Nutr. 2020;112(5):1304–1317.
[24] Metz J. Folate deficiency conditioned by lactation. The American Journal of Clinical Nutrition Volume 23, Issue 6,June 1970, Pages 843-847.
[25] Mackey AD and Picciano MF. Maternal folate status during extended lactation and the effect of supplemental folic acid. Am J Clin Nutr. 1999 Feb;69(2):285-92. doi: 10.1093/ajcn/69.2.285.
[26] Hale, Thomas (2020) Medications and Mothers' Milk online. Accessed 7/31/2025

No additional relevant publications were identified. Publicly available literature restates information presented above.

Reviewer's comment:
The Applicant's review was adequate. The preferential secretion of folic acid into breastmilk will be taken into account by inclusion of a statement in labeling that lactating women treated with this product should follow the U.S. Recommended Dietary Allowances for their condition to ensure that the patient receives adequate folic acid to replenish and maintain her stores.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Labeling for the RS contains no nonclinical toxicology information. As such, the Applicant is relying on published literature to support the nonclinical reproductive toxicology of folic acid. However, the Applicant's Toxicology Written Summary (Module 2.6.6) does not specifically address the effect of folic acid on female and male fertility. Refer to the Pharmacology/Toxicology review by Vanesa Sanchez, PhD and Bo Lee, PhD.

Review of Pharmacovigilance Database

The comparative BA studies conducted by the Applicant in support of the NDA did not evaluate the effect of folic acid on female or male fertility.

Review of Literature

Applicant's Review of Literature

In response to an Information Request, the Applicant conducted a literature search regarding the effects of folic acid on female and male fertility. The Applicant did not provide the search terms used in their review of literature. The search yielded 15 publications. Summaries of publications regarding the effect of folic acid on female fertility are presented in Appendix A and the effect on male fertility in Appendix B of this review.

Based on their review of literature, the Applicant concluded that studies have not demonstrated any adverse effects of folic acid on female or male fertility. The Applicant also noted that the effect of folic acid on fertility in individuals with megaloblastic anemia has not been evaluated in clinical studies.

DPMH Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms "Folic acid" and "fertility", "infertility", "reproduction", "contraception", and "oral contraceptives".

The DPMH review of literature was conducted with assistance from Elsa to assist in the review of some cited publications for relevant content. The content selected for inclusion in this review has been thoroughly reviewed and verified by this reviewer.

The literature review revealed information from a randomized trial in which zinc 66 mg/day and folic acid 5 mg/day were administered orally for 26 weeks. Results from this trial included an increase in sperm count in infertile men receiving this treatment. There was no increase in sperm

count in fertile men.[27] In another study, among couples seeking fertility treatment, men given folic acid 5 mg and elemental zinc 30 mg daily for six months had no improvement in semen quality or live birth rates compared to placebo.[28]

The literature review also revealed information about the effect of folic acid on female fertility. In a study conducted in 259 healthy menstruating women 18 to 44 years of age, dietary folate was associated with increased luteal progesterone concentrations and a lower risk of anovulation.[29] In a study comparing women undergoing infertility treatment with fertile women, folate use and folate status were not associated with improved pregnancy outcomes despite the infertile women using more folate supplements and having better folate status than fertile women.[30]

Additional review of recent published literature revealed no evidence of any adverse effect of folic acid on male and female fertility.

Reviewer's comment:
The Applicant's review was adequate. Although the effect of folic acid on fertility in individuals with megaloblastic anemia has not been evaluated in clinical studies, this reviewer agrees with the Applicant that there appear to be no adverse effects on female or male fertility related to folic acid use. As such, DPMH recommends omission of subsection 8.3 Females and Males of Reproductive Potential.

DISCUSSION AND CONCLUSIONS

Pregnancy

Available data over decades of use of folic acid at recommended doses (0.4-0.8 mg/day) during the preconception period and during pregnancy have not identified an increased risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Although some publications have raised concern about adverse effects of folic acid during pregnancy, these involved folic acid doses > 1 mg/day, with doses as high as 5-10 mg/day in some studies. These concerns are not relevant to this product because the intended population is patients with megaloblastic anemia due to folic acid deficiency, and the maximum recommended dose of Quiofic is 1 mg/day of the folic acid moiety.

Consideration should be given to inclusion of language in subsection 8.1 Pregnancy of labeling for Quiofic stating the risk of neural tube defects associated with inadequate folate intake/levels during the first trimester. Because the safety of folic acid use during pregnancy is well-

[27] Wong W, Merkus H, Thomas C, Menkveld R, Zielhuis G, Steegers-Theunissen R, Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial, Fertil Steril 2002 Mar:77:491-8

[28] Schisterman EF, Sjaarda LA, Clemons T, Carrell DT, Perkins NJ, Johnstone E, Lamb D, et al. 2020. Effect of folic acid and zinc supplementation in men on semen quality and live birth among couples undergoing infertility treatment: a randomized clinical trial. JAMA 323(1): 35-48.

[29] Gaskins AJ, Mumford SL, Chavarro JE, Zhang C, Pollack AZ, Wactawski-Wende J, Perkins NJ, Schisterman EF. 2012. The impact of dietary folate intake on reproductive function in premenopausal women: A prospective cohort study. PLoS One 7(9): e46276, doi: 10.1371/journal.pone.00146276.

[30] Murto T, Kallak TK, Hoas A, Altmae S, Salumets A, Nilsson TK, Skoog Svanberg A, Wanggren K, Ynqve A, Stavreus-Evers A. 2015. Folic acid supplementation and methylenetetrahydrofolate reductase (MTHFR) gene variations in relation to in vitro fertilization pregnancy outcome. Acta Obstet Gynecol Scand 93(1): 65-71.

established, DPMH does not recommend DNH issue a postmarketing requirement (PMR) for pregnancy safety studies for Quiofic. DPMH recommends that pregnancy outcomes in women with megaloblastic anemia treated with Quiofic be monitored via routine pharmacovigilance in the postmarket setting.

Lactation

Levels of folic acid in breastmilk at various stages of lactation have been well characterized, and there is no evidence from over decades of use at recommended doses of any adverse effect on the breastfed infant. There are no data regarding the effect of folic acid on milk production. It is well-established that folate concentrations in breastmilk are maintained even when maternal folate status is compromised. The recommended dietary allowance for folic acid during lactation is discussed above, and a statement will be included in labeling recommending that lactating women treated with this product also follow the U.S. Recommended Dietary Allowances for their condition.

Because the safety of folic acid use during lactation is well-established, DPMH does not recommend DNH issue a PMR for a clinical lactation study for Quiofic. DPMH recommends that adverse events resulting from exposure to Quiofic via breastfeeding be monitored via routine pharmacovigilance in the postmarket setting.

Females and Males of Reproductive Potential

Available data over decades of use of folic acid have not revealed any adverse effects of folic acid on female or male fertility, nor are there any drug interactions between folic acid and oral contraceptives. There is no identified safety signal for embryofetal toxicity that warrants pregnancy testing or recommendations for use of contraception. As such, DPMH recommends omission of subsection 8.3 Females and Males of Reproductive Potential from labeling for Quiofic.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 8.3 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 9/9/2025. DPMH recommendations are below and reflect the discussions with DNH. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published studies over decades of use of folic acid in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnant women should follow the U.S. Recommended Daily Allowances for

pregnancy because their folic acid requirements may exceed those of nonpregnant women. Pregnant women with folic acid deficiency during the first trimester are at increased risk of neural tube defects in the developing fetus. Animal studies to evaluate the potential reproductive and developmental toxicity have not been conducted.

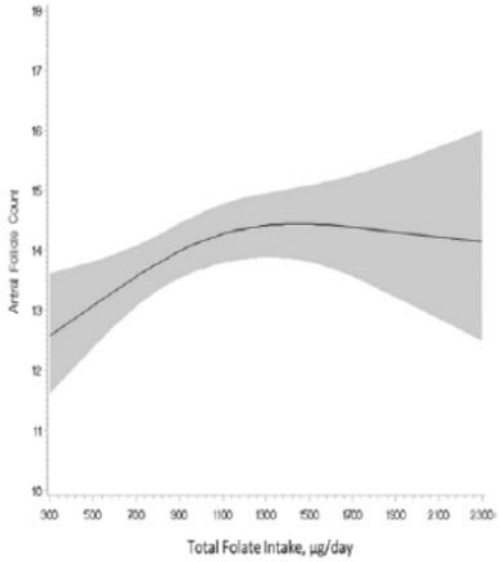
The background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Available data from published studies over decades of use of folic acid supplementation in lactating women have demonstrated that folic acid is present in human milk. Lactating patients should follow the U.S. Recommended Dietary Allowances for their condition, because their folic acid requirements may exceed those of nonlactating patients. At recommended doses, there have been no reports of adverse events in breastfed infants over decades of use. There are no data regarding the effect of folic acid on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for folic acid and any potential adverse effects on the breastfed child from supplemental folic acid or from the underlying maternal condition.

APPENDIX A: Applicant's Review of Published Literature Regarding Effect of Folic Acid on Female Fertility

Author, year	Study design	Number exposed/ unexposed	End points and outcomes of study	Interpretations
Kadir et al., 2022 (1)	Cohort study	552 women seeking infertility treatment (median folate intake 1,005 µg/day)	**There was a positive linear relationship with antral follicle count (AFC) up to approximately 1200 µg/day for total folate intake and up to 800 µg/day for supplemental folate intake without evidence of additional benefit with higher intakes.** 	Higher intake of folate, particularly from supplements, was associated with modestly higher ovarian reserve as measured by AFC among women attending a fertility center.

<table>
<tr><th>Author, year</th><th>Study design</th><th>Number exposed/ unexposed</th><th>End points and outcomes of study</th><th>Interpretations</th></tr>
<tr>
<td>Cueto et al., 2016 (2)</td>
<td>Prospective cohort study</td>
<td>3895 Danish women who were planning a pregnancy between 2007 and 2011</td>
<td>
<table>
<tr><th colspan="7">Fecundability by folic acid supplement use stratified by selected factors (N = 3895)</th></tr>
<tr><th></th><th>Pregnancies</th><th>Cycles</th><th colspan="2">Unadjusted model</th><th colspan="2">Adjusted model</th></tr>
<tr><th></th><th></th><th></th><th>FR</th><th>95% CI</th><th>FR</th><th>95% CI</th></tr>
<tr><td>Irregular periods</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Non-use</td><td>141</td><td>1130</td><td>1</td><td>Ref.</td><td>1</td><td>Ref.</td></tr>
<tr><td>FA-supplement use</td><td>435</td><td>2634</td><td>1.39</td><td>1.16–1.66</td><td>1.35</td><td>1.12–1.65</td></tr>
<tr><td>Regular periods</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Non-use</td><td>591</td><td>3867</td><td>1</td><td>Ref.</td><td>1</td><td>Ref.</td></tr>
<tr><td>FA-supplement use</td><td>1500</td><td>8707</td><td>1.18</td><td>1.08–1.29</td><td>1.11</td><td>1.01–1.22</td></tr>
<tr><td>Cycle length, short (<27 days)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Non-use</td><td>89</td><td>704</td><td>1</td><td>Ref.</td><td>1</td><td>Ref.</td></tr>
<tr><td>FA-supplement use</td><td>227</td><td>1317</td><td>1.47</td><td>1.17–1.85</td><td>1.36</td><td>0.95–1.95</td></tr>
<tr><td>Cycle length, medium (27–29 days)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Non-use</td><td>430</td><td>2785</td><td>1</td><td>Ref.</td><td>1</td><td>Ref.</td></tr>
<tr><td>FA-supplement use</td><td>1090</td><td>6599</td><td>1.14</td><td>1.02–1.26</td><td>1.1</td><td>0.98–1.22</td></tr>
<tr><td>Cycle length ≥30 days</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Non-use</td><td>302</td><td>2212</td><td>1</td><td>Ref.</td><td>1</td><td>Ref.</td></tr>
<tr><td>FA-supplement use</td><td>845</td><td>4742</td><td>1.35</td><td>1.19–1.52</td><td>1.24</td><td>1.10–1.41</td></tr>
</table>
Abbreviations: FR, Fecundability ratio; CI, Confidence interval.
</td>
<td>FA supplementation was associated with increased fecundability, and this association appeared to be stronger among women with irregular cycles and among women with either short or long cycle length.</td>
</tr>
<tr>
<td>Gaskin et al., 2015 (3)</td>
<td>Prospective cohort study</td>
<td>100 women (154 Assisted reproductive technology cycles). Diet was assessed before ART treatment by using a validated food-frequency questionnaire.</td>
<td>
<table>
<tr><th colspan="7">Associations between serum folate and vitamin B-12 concentrations and clinical outcomes after assisted reproduction in 100 women (154 initiated cycles) from the Environment and Reproductive Health Study (2007–2013)</th></tr>
<tr><th rowspan="2">Quartile (minimum-maximum)</th><th colspan="2">Implantation</th><th colspan="2">Clinical pregnancy</th><th colspan="2">Live birth</th></tr>
<tr><th>Cases/Cycle (%)</th><th>RR (95% CI)</th><th>Cases/Cycles (%)</th><th>RR (95% CI)</th><th>Cases/Cycles (%)</th><th>RR (95% CI)</th></tr>
<tr><td>Serum folate, ng/mL</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Q1 (9.7–16.5)</td><td>22/45 (48.9)</td><td>1.00 (ref)</td><td>18/45 (40.0)</td><td>1.00 (ref)</td><td>14/45 (31.1)</td><td>1.00 (ref)</td></tr>
<tr><td>Q2 (16.6–20.2)</td><td>20/35 (57.1)</td><td>1.23 (0.85, 1.77)</td><td>15/35 (42.9)</td><td>1.02 (0.62, 1.67)</td><td>10/35 (28.6)</td><td>0.77 (0.38, 1.54)</td></tr>
<tr><td>Q3 (20.3–26.3)</td><td>23/39 (58.9)</td><td>1.23 (0.90, 1.69)</td><td>22/39 (56.4)</td><td>1.35 (0.90, 2.02)</td><td>17/39 (43.6)</td><td>1.19 (0.68, 2.09)</td></tr>
<tr><td>Q4 (26.4–154.2)</td><td>22/35 (62.9)</td><td>1.31 (0.89, 1.93)</td><td>21/35 (60.0)</td><td>1.50 (0.98, 2.32)</td><td>18/35 (51.4)</td><td>1.62 (0.99, 2.65)</td></tr>
<tr><td>P-trend</td><td></td><td>0.26</td><td></td><td>0.04</td><td></td><td>0.01</td></tr>
</table>
Abbreviations: RR, Relative risk; CI, Confidence interval.
</td>
<td>Serum folate also appears to be beneficial for fertilization. Higher serum concentrations of folate before ART treatment were associated with higher live birth rates among a population exposed to folic acid fortification. These findings support the importance of preconception folic acid supplementation.</td>
</tr>
</table>

<table>
<tr><th>Author, year</th><th>Study design</th><th>Number exposed/ unexposed</th><th>End points and outcomes of study</th><th>Interpretations</th></tr>
<tr><td></td><td></td><td></td><td>
Associations between serum folate and early ART outcomes in 100 women (141 fresh IVF cycles with egg retrieval) from the Environment and Reproductive Health Study (2007–2013)
<table>
<tr><th>Quartile (ng/mL)</th><th>Total oocyte yield (95% CI)</th><th>M2 oocytes (95% CI)</th><th>Fertilization rate (95% CI)</th><th>Proportion with ≥1 best-quality embryo (95% CI)</th></tr>
<tr><td></td><td colspan="4">Adjusted mean (95% CI)</td></tr>
<tr><td>Serum folate, ng/mL</td><td colspan="4"></td></tr>
<tr><td>Q1 (9.7–16.6)</td><td>10.9 (9.3, 12.8)</td><td>9.4 (8.0, 11.2)</td><td>0.59 (0.51, 0.69)</td><td>0.45 (0.32, 0.64)</td></tr>
<tr><td>Q2 (16.6–20.2)</td><td>13.0 (11.2, 15.1)</td><td>11.2 (9.6, 13.0)</td><td>0.65 (0.58, 0.72)</td><td>0.45 (0.30, 0.68)</td></tr>
<tr><td>Q3 (20.3–26.3)</td><td>10.7 (9.0, 12.7)</td><td>8.5 (7.3, 9.9)</td><td>0.69 (0.62, 0.78)</td><td>0.62 (0.46, 0.84)</td></tr>
<tr><td>Q4 (26.4–154.2)</td><td>12.4 (10.0, 15.6)</td><td>10.8 (8.7, 13.5)</td><td>0.70 (0.63, 0.78)</td><td>0.52 (0.38, 0.72)</td></tr>
<tr><td>P-trend</td><td>0.58</td><td>0.61</td><td>0.07</td><td>0.5</td></tr>
</table>
Abbreviations: ART, Assisted Reproductive Technology; CI, Confidence interval.
</td><td></td></tr>
<tr><td>Murto et al., 2014 (4)</td><td>Prospective case–control study</td><td>368 women; 180 women with unexplained infertility in the study group and 188 fertile women in the control group. Folic acid intake was recorded.</td><td>
Pregnancy outcome and questionnaire-based folic acid supplement use
<table>
<tr><th>Parameter</th><th>Folic acid supplement (n = 137)</th><th>No folic acid supplements (n = 42)</th><th>OR (95% CI)</th></tr>
<tr><td>Pregnancy, n (%)</td><td>47 (34.3%)</td><td>16 (38.1%)</td><td>1.010 (0.523–1.952)</td></tr>
<tr><td>Clinical pregnancy, n (%)</td><td>45 (32.8%)</td><td>15 (35.7%)</td><td>1.003 (0.515–1.953)</td></tr>
<tr><td>Miscarriage, n (%)</td><td>12 (8.8%)</td><td>2 (4.8%)</td><td>–</td></tr>
<tr><td>Live birth, n (%)</td><td>33 (24.1%)</td><td>13 (31.0%)</td><td>1.366 (0.677–2.757)</td></tr>
</table>
Abbreviations: OR, Odd ratio; CI, Confidence interval.
Plasma homocysteine concentration and pregnancy outcome according to plasma folate concentration
<table>
<tr><th rowspan="2">Parameter</th><th colspan="2">Plasma folate (nmol/L)</th><th rowspan="2">OR (95% CI)</th></tr>
<tr><th>≥22.5 (n = 78)</th><th><22.5 (n = 89)</th></tr>
<tr><td>Homocysteine (µmol/L), median (range)</td><td>5.9 (2.6–17.2)</td><td>7.4 (3.2–25.8)[a]</td><td>0.803 (0.694–0.930)</td></tr>
<tr><td>Pregnancy, n (%)</td><td>29 (37.2%)</td><td>32 (36.0%)</td><td>0.949 (0.505–1.783)</td></tr>
<tr><td>Clinical pregnancy, n (%)</td><td>28 (35.9%)</td><td>31 (34.8%)</td><td>0.954 (0.505–1.802)</td></tr>
<tr><td>Miscarriage, n (%)</td><td>6 (7.7%)</td><td>7 (7.9%)</td><td>–</td></tr>
<tr><td>Live Birth, n (%)</td><td>22 (28.2%)</td><td>24 (27.0%)</td><td>0.940 (0.476–1.855)</td></tr>
</table>
Abbreviations: OR, Odd ratio; CI, Confidence interval.
a P = 0.003
</td><td>Folic acid supplementation or good folate status did not have a positive effect on pregnancy outcome following infertility treatment in women with unexplained infertility.</td></tr>
<tr><td>Gaskin et al., 2014 (5)</td><td>Prospective cohort study</td><td>232 women with at least one assisted</td><td>Associations between folate intake and clinical outcomes in 232 women (353 initiated cycles) from the environment and reproductive health study</td><td>Live birth rate was higher among women in the highest quartile of supplement folate intake</td></tr>
</table>

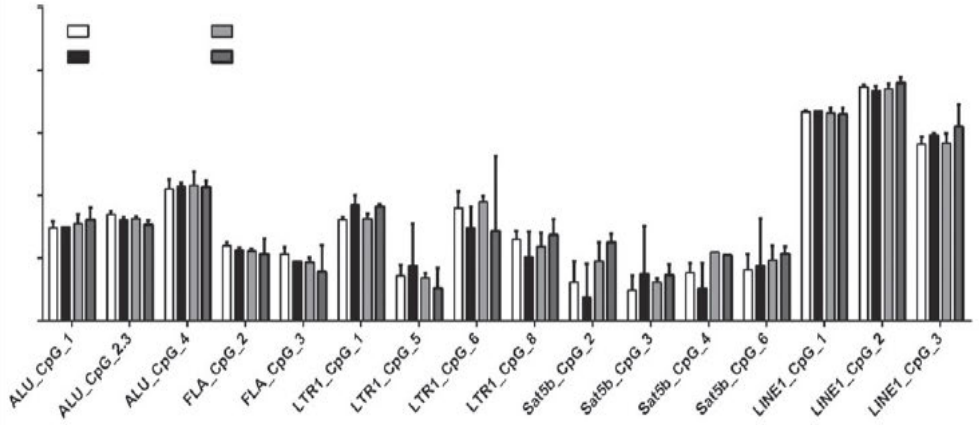
Author, year	Study design	Number exposed/ unexposed	End points and outcomes of study				Interpretations
		reproductive technology cycle. Diet (median folate intake=1,778 µg/day) was assessed before assisted reproductive technology treatment using a validated food frequency	**Quartile (range, µg/day)**	**Implantation rate (95% CI)**	**Clinical pregnancy rate (95% CI)**	**Live birth rate (95% CI)**	(>800µg/day). Higher intake of supplemental folate was associated with higher live birth rates and low cycle failure rate after embryo transfer.
				Adjusted mean (95% CI)			
			Total folate (in DFE)				
			Q1 (<1262)	0.46 (0.35, 0.57)	0.39 (0.29, 0.51)	0.30 (0.21, 0.42)	
			Q2 (1262–1778)	0.62 (0.50, 0.72)	0.56 (0.44, 0.67)*	0.47 (0.35, 0.59)*	
			Q3 (1779–2352)	0.64 (0.51, 0.74)*	0.58 (0.46, 0.70)*	0.42 (0.30, 0.55)	
			Q4 (>2352)	0.68 (0.57, 0.78)*	0.63 (0.52, 0.74)*	0.56 (0.43, 0.67)*	
			P trend	0.01	0.007	0.01	
			Supplemental folate				
			Q1 (<400)	0.43 (0.31, 0.55)	0.41 (0.29, 0.53)	0.35 (0.24, 0.48)	
			Q2 (400–543)	0.66 (0.55, 0.75)*	0.55 (0.44, 0.65)	0.43 (0.32, 0.54)	
			Q3 (544–800)	0.58 (0.46, 0.70)	0.55 (0.42, 0.66)	0.39 (0.28, 0.52)	
			Q4 (>800)	0.67 (0.56, 0.77)*	0.62 (0.51, 0.73)*	0.55 (0.43, 0.66)*	
			P trend	0.03	0.03	0.07	
			Food folate				
			Q1 (<371)	0.58 (0.47, 0.69)	0.47 (0.36, 0.58)	0.35 (0.25, 0.47)	
			Q2 (372–436)	0.55 (0.44, 0.66)	0.51 (0.40, 0.63)	0.41 (0.30, 0.52)	
			Q3 (437–534)	0.61 (0.49, 0.71)	0.56 (0.45, 0.67)	0.49 (0.37, 0.60)	
			Q4 (>534)	0.64 (0.52, 0.75)	0.60 (0.48, 0.71)	0.49 (0.37, 0.61)	
			P trend	0.35	0.1	0.08	
			*Indicates a P value <0.05 comparing that quartile vs. first quartile. Abbreviations: CI, Confidence interval; DFE, Dietary folate equivalents.				

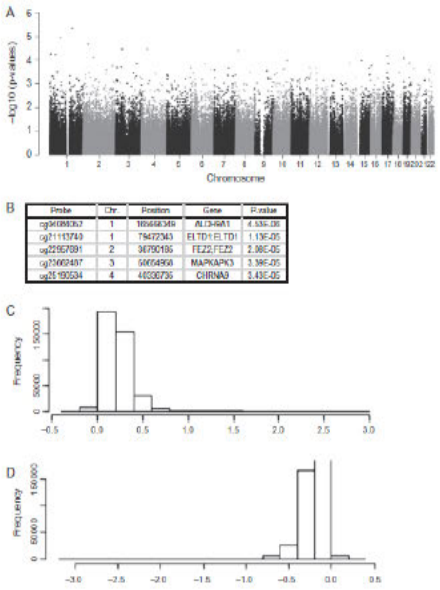
Associations between folate intake and early ART outcomes in 222 women (289 fresh IVF cycles with egg retrieval) from the Environment and Reproductive Health Study

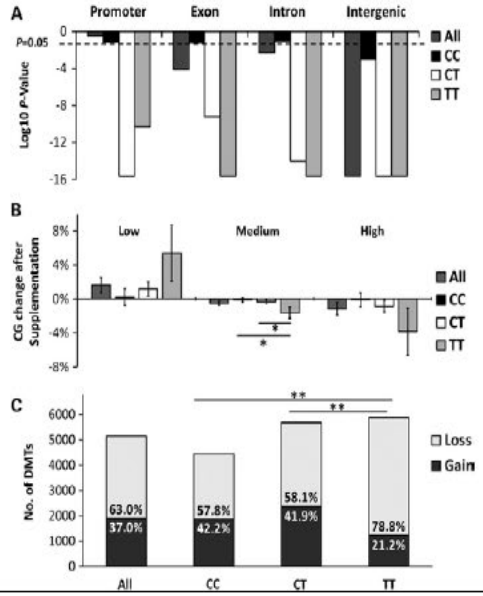
Quratile (median, µg/day)	Total oocyte yield (95% CI)	M2 oocytes	Fertilization rate	% With ≥1 best quality embryo on day 2 & 3
	Adjusted mean (95% CI)			
Total folate (in DFE)				
Q1 (<1262)	11.5 (10.3, 12.9)	10.0 (9.0, 11.1)	0.70 (0.64, 0.75)	62 (48, 74)
Q2 (1262–1778)	9.9 (8.9, 11.1)	8.8 (7.9, 9.9)	0.69 (0.63, 0.74)	62 (48, 74)
Q3 (1779–2352)	11.3 (10.1, 12.6)	9.2 (8.2, 10.3)	0.72 (0.67, 0.78)	60 (46, 73)
Q4 (>2352)	10.3 (9.2, 11.5)	8.7 (7.8, 9.7)	0.76 (0.71, 0.81)	68 (55, 79)
P trend	0.48	0.16	0.06	0.54

<table>
<tr><th>Author, year</th><th>Study design</th><th>Number exposed/ unexposed</th><th>End points and outcomes of study</th><th>Interpretations</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Supplemental folate</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Q1 (<400)</td><td>12.1 (10.9, 13.6)</td><td>10.7 (9.6, 11.9)</td><td>0.68 (0.62, 0.73)</td><td>62 (47, 74)</td></tr>
<tr><td>Q2 (400–543)</td><td>10.3 (9.3, 11.5)*</td><td>8.8 (7.9, 9.8)*</td><td>0.70 (0.65, 0.75)</td><td>58 (45, 70)</td></tr>
<tr><td>Q3 (544–800)</td><td>10.3 (9.1, 11.5)*</td><td>8.6 (7.7, 9.6)*</td><td>0.73 (0.67, 0.78)</td><td>68 (53, 79)</td></tr>
<tr><td>Q4 (>800)</td><td>10.4 (9.4, 11.6)</td><td>8.8 (8.0, 9.8)*</td><td>0.76 (0.71, 0.80)*</td><td>65 (52, 77)</td></tr>
<tr><td>P trend</td><td>0.08</td><td>0.02</td><td>0.03</td><td>0.42</td></tr>
<tr><td>Food Folate</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Q1 (<371)</td><td>11.0 (9.9, 12.3)</td><td>9.4 (8.4, 10.5)</td><td>0.68 (0.62, 0.74)</td><td>56 (42, 69)</td></tr>
<tr><td>Q2 (372–436)</td><td>10.4 (9.3, 11.6)</td><td>8.9 (7.9, 9.9)</td><td>0.74 (0.68, 0.79)</td><td>71 (58, 81)</td></tr>
<tr><td>Q3 (437–534)</td><td>9.8 (8.8, 11.0)</td><td>8.4 (7.5, 9.4)</td><td>0.75 (0.69, 0.80)</td><td>68 (54, 79)</td></tr>
<tr><td>Q4 (>534)</td><td>11.7 (10.5, 13.1)</td><td>10.0 (9.0, 11.2)</td><td>0.71 (0.65, 0.76)</td><td>57 (43, 71)</td></tr>
<tr><td>P trend</td><td>0.36</td><td>0.35</td><td>0.78</td><td>0.85</td></tr>
</table>
Abbreviations: CI, Confidence interval; ART, Assisted reproductive technology; DFE, Dietary folate equivalents; M2, Mature oocytes.
* Indicates a P value < 0.05 comparing that quartile vs. first quartile.
</td><td></td></tr>
<tr><td>Gaskins et al., 2012 (6)</td><td>Prospective cohort study</td><td>259 healthy premenopausal women Followed for one (n= 9) or two (n= 250) menstrual cycles years from the western New York region for up to 2 menstrual cycles. Total folate and specific sources of folate were assessed up to 4 times per cycle by 24-hour recall.</td><td>
<table>
<tr><td colspan="5">Association between dietary folate intake and estradiol and progesterone in the BioCycle Study</td></tr>
<tr><td>Tertile (Median)</td><td>Hormone</td><td>% Change</td><td>95% CI</td><td>P for trend</td></tr>
<tr><td colspan="5">Synthetic folate (µg/day)</td></tr>
<tr><td>1 (100.9)</td><td>Estradiol</td><td>REF</td><td>REF</td><td rowspan="3">0.56</td></tr>
<tr><td>2 (157.9)</td><td>Estradiol</td><td>-6.09</td><td>(-16.45, 5.55)</td></tr>
<tr><td>3 (270.6)</td><td>Estradiol</td><td>2.33</td><td>(-7.04, 12.64)</td></tr>
<tr><td>1 (100.9)</td><td>Progesterone</td><td>REF</td><td>REF</td><td rowspan="3">0.05</td></tr>
<tr><td>2 (157.9)</td><td>Progesterone</td><td>12.01</td><td>(−4.03, 30.74)</td></tr>
<tr><td>3 (270.6)</td><td>Progesterone</td><td>15.70</td><td>(0.05, 33.80)</td></tr>
</table>
Abbreviations: CI, Confidence interval.
</td><td>A diet high in synthetic folate may be associated with increased progesterone levels and lower risk of sporadic anovulation. Further study of the effect of dietary folate and folic acid supplement use on reproductive health is warranted.</td></tr>
</table>

Appendix B: Applicant's Review of Published Literature Regarding Effect of Folic Acid on Male Fertility

Author, year	Study design	Number exposed/ unexposed	End points and outcomes of study	Interpretations
Chan et al., 2017 (7)	Control versus treatment study of genome-wide sperm DNA methylation patterns	Men with no history of infertility received placebo (n = 9) or supplement containing 400 µg folic acid/day (n = 10) for short-term (90-day) exposure	**MassArray Epityper analysis of repeat regions averaged over individual participants (n = 3 per group/time point) did not reveal alterations in sperm DNA methylation patterns after 90-day treatment with placebo or folic acid supplement. Mean (±SEM).** 	Short-term exposure to low-dose folic acid supplements of 400 µg/day, over a period of 3 months, a duration of time that might occur during infertility treatments, has no major impact on the sperm DNA methylome.

Author, year	Study design	Number exposed/ unexposed	End points and outcomes of study	Interpretations
			450 K array probe analysis and equivalence testing demonstrate no differences in DNA methylation between groups (n = 9 placebo, n = 10 supplemented) following 90-day treatments. (A) Negative log P-values were plotted along the entire chromosome following paired t-tests comparing differences in β-values observed between placebo and supplemented groups following 90-day intervention. (B) The top five probes/CpGs found to differ between groups are listed; however, significant changes were not observed following normalization and correction for multiple comparisons. The (C) upper and (D) lower confidence intervals following equivalence testing are depicted, which demonstrate that large differences between supplement and placebo subjects were unlikely. 	

Author, year	Study design	Number exposed/ unexposed	End points and outcomes of study	Interpretations
Aarabi et al., 2015 (8)	NR	30 healthy normozoospermic men presenting with idiopathic infertility received high-dose folic acid supplementation (5 mg/day) for 6 months	**Global loss of methylation was detected by reduced representation bisulfite sequencing (RRBS) among different genomic regions after supplementation with high-dose folic acid. (A) Bars indicate the log10 of the P-value for the significant global loss of methylation across all RRBS sequenced tiles. Data for all participants and the methylenetetrahydrofolate reductase (MTHFR) C677T genotypes are presented. Patients with MTHFR 677TT genotype demonstrated the most significant loss of methylation. (B) RRBS sequenced CGs were calculated and classified as low (<20% methylation), medium or intermediate (20–80% methylation) and high (>80% methylation). Bars indicate the relative change in class after supplementation for all participants and the MTHFR C677T genotypes. MTHFR 677TT participants demonstrated the most diverse and greatest changes in terms of an increase in CGs with low methylation and decrease in CGs with medium and high methylation levels. (C) The mean number of DMTs with greater than 10% change of methylation levels is depicted for all participants and the MTHFR C677T genotypes. The percentage of tiles with loss or gain of methylation is shown. Asterisks indicate significant differences between groups (ANOVA for B and Fisher's exact test for C; P<0.05 for one asterisk and P<0.0001 for two asterisks).**  	The most marked loss of DNA methylation was found in sperm from patients homozygous for the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, a common polymorphism in a key enzyme required for folate metabolism. Our data reveal alterations of the human sperm epigenome associated with high-dose folic acid supplementation, effects that were exacerbated by a common polymorphism in MTHFR.

<table>
<tr><th>Author, year</th><th>Study design</th><th>Number exposed/ unexposed</th><th>End points and outcomes of study</th><th>Interpretations</th></tr>
<tr>
<td>Boonyarangkul et al., 2015 (9)</td>
<td>Double-blind, randomized, control trial</td>
<td>68 subfertile men were randomized into 4 groups: control, Tamoxifen, Folic acid (5 mg/day), Folic acid + Tamoxifen and treated for 3 months</td>
<td>
Comparisons of semen parameters (concentration, motility and morphology) and semen viability (hypo-osmotic swelling test, HOS), hyaluronan binding assay (HBA), and DNA damage (COMET test) between control group and three treatment groups of before, after 3 months of treatment completed and after 3 months discontinuation of treatment
<table>
<tr><th>Parameters</th><th>Control</th><th>Folate</th></tr>
<tr><td>Concentration (million/ml)</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>92.57 ± 13.99</td><td>61.50 ± 6.02</td></tr>
<tr><td>3-month</td><td>76.24 ± 13.10</td><td>66.58 ± 7.70</td></tr>
<tr><td>6-month</td><td>76.13 ± 18.29</td><td>53.30 ± 5.88</td></tr>
<tr><td>Motility (%)</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>14.33 ± 2.44</td><td>11.40 ± 2.41</td></tr>
<tr><td>3-month</td><td>18.06 ± 3.46</td><td>20.40 ± 3.97*</td></tr>
<tr><td>6-month</td><td>17.33 ± 4.28</td><td>15.00 ± 2.61</td></tr>
<tr><td>Morphology (%)</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>2.20 ± 0.48</td><td>2.06 ± 0.70</td></tr>
<tr><td>3-month</td><td>1.60 ± 0.51</td><td>1.46 ± 0.40</td></tr>
<tr><td>6-month</td><td>1.40 ± 0.37</td><td>1.46 ± 0.40</td></tr>
<tr><td>Semen viability (hypo-osmotic swelling test, HOS)</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>44.62 ± 5.16</td><td>38.54 ± 6.27</td></tr>
<tr><td>3-month</td><td>48.60 ± 5.95</td><td>50.33 ± 5.07</td></tr>
<tr><td>6-month</td><td>44.32 ± 5.71</td><td>46.50 ± 4.71</td></tr>
<tr><td>Semen viability (hyaluronan binding assay (HBA)</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>45.11 ± 8.14</td><td>54.55 ± 8.68</td></tr>
<tr><td>3-month</td><td>41.73 ± 6.90</td><td>66.08 ± 6.44**</td></tr>
<tr><td>6-month</td><td>40.6 ± 7.03</td><td>54.98 ± 6.70</td></tr>
<tr><td>DNA damage (COMET test)</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>11.16 ± 4.14</td><td>14.59 ± 5.15</td></tr>
<tr><td>3-month</td><td>10.08 ± 3.39</td><td>4.04 ± 0.94*</td></tr>
<tr><td>6-month</td><td>8.69 ± 4.28</td><td>6.01 ± 1.49</td></tr>
</table>
* Significantly difference from pretreatment (p-value <0.05)
** Significantly difference from control group (p-value <0.05)
</td>
<td>Sperm motility increased significantly at 3 months following folic acid treatment compared to the control group. However, sperm morphology did not show statistically significant differences between the folic acid and the control groups. DNA damage, assessed by DNA tail length, decreased significantly in the folic acid group compared to the control group at 3 months.</td>
</tr>
</table>

<table>
<tr><th>Author, year</th><th>Study design</th><th>Number exposed/ unexposed</th><th>End points and outcomes of study</th><th>Interpretations</th></tr>
<tr><td>Raigani et al., 2013 (10)</td><td>Double-blind, randomized, clinical trial</td><td>83 subfertile oligoasthenoteratozoospermic men were randomized into 4 groups: two capsule per day as folic acid (5mg/day)/placebo (n=20), folic acid + Zinc (n=21), Zinc/placebo (n=24), placebo/placebo (n=18) and treated for 16 weeks</td><td>
Pre-intervention and post-intervention comparisons of sperm parameters between folic acid and placebo group
<table>
<tr><th rowspan="2">Parameters</th><th colspan="2">Folic acid/Placebo (n = 20)</th><th colspan="2">Placebo/Placebo (n = 18)</th></tr>
<tr><th>Preintervention</th><th>Post-intervention</th><th>Preintervention</th><th>Post-intervention</th></tr>
<tr><td>Sperm concentration (× 10^6 cells/mL)</td><td>11.5 (7.5–17.9)</td><td>15 (9.7–24)</td><td>11.6 (8.3–13.5)</td><td>12 (7.5–27.3)</td></tr>
<tr><td>Sperm motility (%)</td><td>34.5 (13.7–53.7)</td><td>35 (15–50)</td><td>35 (20–47.5)</td><td>35 (21–42.5)</td></tr>
<tr><td>Sperm abnormal morphology (%)</td><td>95 (92–97.7)</td><td>94 (91–97)</td><td>94.5 (88.7–98)</td><td>94 (91–97)</td></tr>
<tr><td>Sperm DNA damage (AO) (%)</td><td>31.7 ± 14.8</td><td>24.3 ± 12</td><td>34.5 ± 19.7</td><td>29.5 ± 10</td></tr>
<tr><td>Sperm chromatin abnormal maturity (AB) (%)</td><td>30.1 ± 8.8</td><td>29.8 ± 7.4</td><td>36.2 ± 18.1</td><td>31.4 ± 9.2</td></tr>
<tr><td>Sperm chromatin abnormal maturity (AB) (%)</td><td>30.1 ± 8.8</td><td>29.8 ± 7.4</td><td>36.2 ± 18.1</td><td>31.4 ± 9.2</td></tr>
<tr><td>Sperm chromatin abnormal integrity (TB) (%)</td><td>33.8 ± 7.5</td><td>33.1 ± 8.2</td><td>40.3 ±18.1</td><td>38.9 ± 14.5</td></tr>
<tr><td>CMA3-positive sperm (%)</td><td>32.1 ± 12.9</td><td>33.1 ± 8.6</td><td>41 ± 15.3</td><td>41.5 ±13.9</td></tr>
<tr><td>Rho123- positive sperm (%)</td><td>33.2 ± 13.9</td><td>35.9 ± 18.2</td><td>34 ± 17.5</td><td>30.1 ± 15.6</td></tr>
<tr><td>Eosin-Nigrosin-stained sperm (%)</td><td>50.1 ± 17.6</td><td>47.2 ± 8.7</td><td>62.6 ± 20.2</td><td>55.4 ± 21</td></tr>
</table>
</td><td>Folic acid supplementation demonstrated no significant advantage across most semen parameters compared to placebo.</td></tr>
<tr><td>da Silva et al, 2013 (11)</td><td>Double-blind, randomized, placebo-controlled trial</td><td>49 subfertile men were randomized into 2 groups: Folic acid, or control and treated for 3 months</td><td>
Comparability of the sperm parameters between the folic acid and placebo group
<table>
<tr><th>Parameters</th><th>Folic acid (n=23)</th><th>Placebo (n=26)</th><th>P-value</th></tr>
<tr><td>Concentration (× 10^6 cells/mL)</td><td>25.9 (1–108)</td><td>20.8 (1–64)</td><td>0.17</td></tr>
<tr><td>Motility (%)</td><td>46.5 (20–70)</td><td>49.2 (25–80)</td><td>0.46</td></tr>
<tr><td>Morphology (%)</td><td>23.3 (20–30)</td><td>22.3 (15–30)</td><td>0.09</td></tr>
<tr><td>Vitality (%)</td><td>66.7 (50–80)</td><td>65.8 (45–85)</td><td>0.41</td></tr>
</table>
</td><td>There was no statistically significant improvement in the concentration, motility, morphology, or vitality of spermatozoa in the folic acid group compared to the placebo groups.</td></tr>
<tr><td>Wong et al., 2002 (12)</td><td>Double-blind, randomized, placebo-controlled trial</td><td>108 fertile and 103 subfertile men were randomized into 4 groups: Folic acid (5 mg/day) /placebo, Zinc/placebo, Folic acid + Zinc, placebo/placebo for up to 26 weeks.</td><td>
Pre-intervention and post-intervention comparisons of sperm parameters between folic acid and placebo group
<table>
<tr><th rowspan="2">Parameters</th><th colspan="2">Placebo (n = 25)</th><th colspan="2">Folic acid (n = 22)</th></tr>
<tr><th>Preintervention</th><th>Post-intervention</th><th>Preintervention</th><th>Post-intervention</th></tr>
<tr><td colspan="5">Sperm concentration (10^6 cells/mL)[a]</td></tr>
<tr><td>Subfertile men</td><td>7.5 (0.7–110)</td><td>9 (0.8–80)</td><td>10 (1.4–110)</td><td>14 (0.9–130)</td></tr>
<tr><td>Fertile men</td><td>90 (1.3–200)</td><td>85 (9–225)</td><td>70 (16–155)</td><td>70 (0–155)</td></tr>
<tr><td>Motility (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subfertile men</td><td>30 (2–70)</td><td>30 (5–80)</td><td>30 (2–60)</td><td>35 (5–65)</td></tr>
<tr><td>Fertile men</td><td>60 (20–80)</td><td>55 (25–80)</td><td>60 (30–80)</td><td>58 (30–75)</td></tr>
<tr><td colspan="5">Morphology (%)</td></tr>
</table>
</td><td>Folic acid supplementation resulted in no significant changes in semen variables (i.e. sperm concentration, % of abnormal spermatozoa, total normal sperm count), except for morphology as determined according to strict criteria, which is slightly decreased in the folic acid group.</td></tr>
</table>

Author, year	Study design	Number exposed/ unexposed	End points and outcomes of study					Interpretations
			WHO criteria (abnormal)[a]					
			Subfertile men	80 (53–98)	79 (61–98)	79 (56–94)	81 (66–93)	
			Fertile men	58 (37–91)	62 (38–87)	64 (34–90)	66 (35–86)	
			Strict criteria (normal)					
			Subfertile men	2 (1–9)	2 (1–8)	2 (1–12)	2 (1–5)[b]	
			Fertile men	5 (1–12)	5 (1–10)	5 (1–15)	5 (1–17)	
			Total normal sperm count ($\times 10^6$cells/mL)					
			Subfertile men	6.4 (0.3–113)	6.3 (0.1–80)	8 (0.7–61)	9.1 (0.8–32)	
			Fertile men	126 (0.3–414)	76.2 (4.8–547)	68.6 (14.4–410)	89.8 (13.7–167)	
			Mean (± SD) volume (mL)					
			Subfertile men	3.9 ± 1.3	3.2 ± 1.3	3.8 ± 1.7	3.3 ± 1.3	
			Fertile men	3.6 ±1.8	3.4 ± 2.2	3.7 ± 1.9	3.4 ± 1.8	
			a Determination according to World Health Organization criteria (1992). Normal reference values are sperm concentration of 20×10^6cells/mL, motility >50% and morphology <70% abnormal. b P<.05 for comparison between baseline and post-treatment values. Abbreviations: SD, Standard deviation.					
Animal Studies								
Author, year	**Findings**							
Ly et al., 2017 (13)	Folic acid deficiency and high dose supplementation can be detrimental to germ cell development and reproductive fitness, in part by altering DNA methylation in sperm.							
Lambrot et al. 2013 (14)	Using in an inbred C57BL/6 mouse model that was exposed to low dietary folate beginning in utero and throughout life, it is concluded that paternal diet alters sperm DNA methylation and is associated with negative reproductive outcomes including birth defects in offspring.							

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/s/

KEVIN L CLARK
10/01/2025 09:06:55 AM

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LYNNE P YAO
10/01/2025 09:35:58 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/29/2025

TO: Division of Non-Malignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216395

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4). The RRA was conducted under the following submission: ANDA (b) (4).

OSIS concluded that data from the reviewed study was reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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/s/

FOLAREMI ADEYEMO
05/29/2025 01:32:32 PM