Clinical Review of 505(b)(2) Application

Submission Date	March 26, 2025
NDA#	216395
SD#	1
Drug Name: Non-Proprietary (Proprietary, if appl.)	Folic Acid Oral Solution, 1 mg/5 mL; QUIOFIC®
Indication(s) Sought	• QUIOFIC is a folate analog indicated for the treatment of megaloblastic anemias due to folic acid deficiency in adult and pediatric patients.
Clinical Reviewer	Patricia Oneal, MD
Clinical Team Leader	Margaret Thompson, MD, PhD

Actions Recommended: Approval

Background of Application:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, CMP Development, LLC has submitted NDA 216395 for folic acid (QUIOFIC®) 1 mg/5 mL oral solution. The Applicant's proposed formulation of folic acid is an oral solution. This submission relies on safety and efficacy findings of the discontinued listed drug (LD) folic acid (Folvite) tablets which was approved in 1947 under NDA 005897 held by Wyeth Pharmaceuticals. It is listed in the Orange Book as Discontinued-not for safety or efficacy reasons. The Applicant has conducted bioavailability/bioequivalence (BA/BE) studies relying on the Orange Book reference standard (RS) Folic Acid Tablets, 1 mg, supplied by Amneal Pharmaceuticals for a comparison bridge to the Folvite Tablets. The reference standard (RS) is the folic acid tablet, 1 mg, supplied by Amneal Pharmaceuticals (ANDA 040625) as of July 21, 2005.

Documents Reviewed:

SD-1 (Receipt Date: March 26, 2025)

Module 1

- Forms
- Cover Letter
- Administrative Information
    - Financial Certification and Disclosure
    - Patent and Exclusivity
- Correspondence regarding Meetings
- Proposed Pediatric Study Request and Amendments
- Labeling (draft, annotated and Listed Drug Labeling)

Module 2

- Introduction

- Quality Overview Summary
- Nonclinical Overview
- Clinical Overview
- Clinical Summary

Module 5

- Clinical Study Reports
- Comparative BA and Bioequivalence (BE) Study Reports
    - Project No. 007-24: Open label, randomized, balanced, two treatments, three period, three sequence, partial replicate, crossover, single dose, oral comparative bioavailability study for Folic acid 1 mg/5 mL oral solution (Test Product) of CMP Development LLC and Folic acid 1 mg tablet of Amneal Pharmaceuticals (Reference Product) in healthy, adult, human subjects under fasting condition
    - Project No. 008-24: Open label, randomized, balanced, two treatments, three period, three sequence, partial replicate, crossover, single dose, oral comparative bioavailability study for Folic acid 1 mg/5 mL oral solution (Test Product) of CMP Development LLC and Folic acid 1 mg tablet of Amneal Pharmaceuticals (Reference Product) in healthy, adult, human subjects under fed condition

Literature Review: *A literature review for new safety information regarding folic acid was conducted to determine whether the current labeling was sufficient to provide adequate instructions for use. There was no evidence of any new safety findings regarding folic acid.*
The Sponsor conducted two bioavailability studies to assess the exposure of folic acid between oral solution and tablets. Under fasting conditions, the exposure of folic acid from the oral solution product was greater than the reference folic acid tablets. The wide safety margin of folic acid is not clinically significant since it is renally excreted. The potential risk of administration of folic acid alone is when Vitamin B12 is deficient which could result in irreversible neurological damage.
The application does rely on published literature to support the efficacy of folic acid oral tablets, 1 mg, for its approved indications. The applicant is using the safety and effectiveness data from the reference standard (RS) folic acid tablet, 1 mg, supplied by Amneal Pharmaceuticals.

Review of other Folic Acid Labelings:
There are 7 actively marketed ANDAs for Folic acid oral tablets (1 mg). Their numbers are A091145, A040625, A210064, A202437, A090035, A040796, A204418 and A080680. The Applicant has reported that ANDA 080680 is not available for comparative purposes; hence, ANDA 040625 was selected to be used as the reference product in this application. This ANDA has not been discontinued.

Summary of Published Literature Findings:
This reviewer conducted a PubMed database search for recent publications regarding folic acid safety, and no new issues were identified.

Clinical Efficacy Studies:
There were no clinical efficacy studies performed for Folic Acid Oral Solution (1 mg / 5 mL) due to the Applicant's reliance on the established efficacy of the RLD and RS Folic Acid Oral Tablets 1 mg, to which Folic Acid Oral Solution (1 mg / 5 mL) is bioequivalent in all clinically relevant measurements.

Bioavailability of Folic Acid Oral Solution, 1 mg/5 mL and its unintended effects:
Review of the bioavailability studies of folic acid oral solution in healthy, adult human subjects under fasting and fed conditions demonstrated higher bioavailability compared to the reference tablets under fasting conditions. Under fed conditions, the test product had modestly lower exposures compared to the reference tablets (*see Clinical Pharmacology Review dated January 16, 2026).*

Because of the higher bioavailability seen in healthy adults under fasting conditions, concerns of potential adverse effects of excess folic acid have been raised. Folate blood test levels above 20 ng/mL are generally considered an elevated level of folic acid. For adults, including pregnant and lactating women, the upper limit (UL) for folic acid from supplements and fortified foods is 1,000 micrograms (µg) or 1 milligram (mg) daily.

While the intestines and liver convert ingested folic acid into usable, natural folate, this metabolic pathway is easily saturated. Consequently, high doses of synthetic folic acid—commonly found in supplements—can lead to elevated levels of "unmetabolized folic acid" (UMFA) in the blood. While this can correct the megaloblastic anemia caused by a Vitamin B12 deficiency, it does not stop the

underlying damage. Critically, this "masked" deficiency allows neurological damage from low B12 to progress, which can become irreversible if left untreated [1,2,3].

The Division agrees with the including the potential risk of administration of folic acid alone is improper therapy for pernicious anemia and other megaloblastic anemias in which Vitamin B12 is deficient into Section 5 of the USPI of Warnings and Precautions.

Orange Book Status/Outstanding Exclusivities for Approved NDAs:
Upon review of this application, there were no outstanding exclusivities for the approved ANDAs.

[1] Maruvada P, Stover PJ, Mason JB, Bailey RL, Davis CD, Field MS, Finnell RH, Garza C, Green R, Gueant JL, Jacques PF, Klurfeld DM, Lamers Y, MacFarlane AJ, Miller JW, Molloy AM, O'Connor DL, Pfeiffer CM, Potischman NA, Rodricks JV, Rosenberg IH, Ross SA, Shane B, Selhub J, Stabler SP, Trasler J, Yamini S, Zappalà G. Knowledge gaps in understanding the metabolic and clinical effects of excess folates/folic acid: a summary, and perspectives, from an NIH workshop. Am J Clin Nutr. 2020 Nov 11;112(5):1390-1403.

[2] Regan L Bailey, Kevin W Dodd, Jaime J Gahche, Johanna T Dwyer, Margaret A McDowell, Elizabeth A Yetley, Christopher A Sempos, Vicki L Burt, Kathy L Radimer, Mary Frances Picciano, Total folate and folic acid intake from foods and dietary supplements in the United States: 2003–2006123, The American Journal of Clinical Nutrition,
Volume 91, Issue 1, 2010, 231-237.

[3] Sweeney, M.R., McPartlin, J. & Scott, J. Folic acid fortification and public health: Report on threshold doses above which unmetabolised folic acid appear in serum. BMC Public Health 7, 41 (2007).

Labeling:
The labeling was submitted in PLR and PLLR format. We have had five multidisciplinary labeling meetings held on August 26, 2025, September 9, 2025, October 1, 2025, and October 29, 2025.

On November 11, 2020, the Agency agreed on the Initial Pediatric Study Plan (Agreed iPSP) for folic acid oral solution for the treatment of anemias of nutritional origin, pregnancy, infancy, or childhood. On December 2, 2025, the Pediatric Review Committee (PeRC) agreed this product is assessed in pediatric patients 0 to <18 years of age for treatment of megaloblastic anemias due to folic acid deficiency in adult and pediatric patients.

Regulatory Conclusion:

There was no clinical data submitted in this 505(b)(2) application for NDA 216395 Folic Acid Oral Solution, 1 mg/5 mL. The Applicant has referenced the FDA's findings of clinical safety and effectiveness of the RLD Folic acid 1 mg tablet (ANDA 040625).

The Division agrees with including that high folic acid levels can mask the symptoms of Vitamin B12 deficiency as a potential risk into Section 5 of the USPI of Warnings and Precautions.

Based on my review, I recommend granting approval for NDA 216395 Folic Acid Oral Solution, 1 mg/5 mL for treatment of megaloblastic anemias due to folic acid deficiency in adult and pediatric patients.

The Application is pending assessment by the 505(b)2 review committee.

References:

1. Maruvada P, Stover PJ, Mason JB, Bailey RL, Davis CD, Field MS, Finnell RH, Garza C, Green R, Gueant JL, Jacques PF, Klurfeld DM, Lamers Y, MacFarlane AJ, Miller JW, Molloy AM, O'Connor DL, Pfeiffer CM, Potischman NA, Rodricks JV, Rosenberg IH, Ross SA, Shane B, Selhub J, Stabler SP, Trasler J, Yamini S, Zappalà G. Knowledge gaps in understanding the metabolic and clinical effects of excess folates/folic acid: a summary, and perspectives, from an NIH workshop. Am J Clin Nutr. 2020 Nov 11;112(5):1390-1403.
2. Regan L Bailey, Kevin W Dodd, Jaime J Gahche, Johanna T Dwyer, Margaret A McDowell, Elizabeth A Yetley, Christopher A Sempos, Vicki L Burt, Kathy L Radimer, Mary Frances Picciano, Total folate and folic acid intake from foods and dietary supplements in the United States: 2003–2006, The American Journal of Clinical Nutrition, Volume 91, Issue 1, 2010, 231-237.
3. Sweeney, M.R., McPartlin, J. & Scott, J. Folic acid fortification and public health: Report on threshold doses above which unmetabolised folic acid appear in serum. BMC Public Health 7, 41 (2007).
4. Miller JW, Smith A, Troen AM, Mason JB, Jacques PF, Selhub J. Excess Folic Acid and Vitamin B12 Deficiency: Clinical Implications? Food Nutr Bull. 2024 Jun;45(1_suppl): S67-S72.
5. Berry RJ. Lack of historical evidence to support folic acid exacerbation of the neuropathy caused by vitamin B12 deficiency. Am J Clin Nutr. 2019 Sep 1;110(3):554-561.
6. Baddam S, Khan KM, Jialal I. Folic Acid Deficiency. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 January.

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