CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216395Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	216395
Link to EDR	\\CDSESUB1\evsprod\NDA216395\0001
Submission Date	03/26/2025
Submission Type	505 (b)(2)
PDUFA Goal Date	1/26/2026
Brand Name	QUIOFIC
Generic Name	Folic acid
Dosage Form and Strength	Oral solution, 1 mg/5 mL
Route of Administration	Oral
Proposed Indications	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.
Proposed Dosage Regimen	Same as listed drug, FOLVITE (see Section 2.1.5)
Applicant	CMP Development LLC.
OCP Review Team	Ritika Kurian, Ph.D., Sudharshan Hariharan, Ph.D.

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1 EXECUTIVE SUMMARY

The Applicant, CMP Development LLC., submitted this 505 (b)(2) application for Folic Acid Oral Solution (1 mg/ 5ml), intending to seek approval for the same indications as the Listed Drug (LD) Folvite (folic acid tablets, 1 mg). The Applicant proposes to rely on FDA's previous findings of safety and efficacy of the Listed Drug (LD) Folvite (folic acid 1 mg tablets) approved under NDA # 005897. The LD is not currently marketed.

The main objective of this review is to evaluate whether the bioequivalence studies conducted for folic acid oral solution establishes an adequate scientific bridge to the LD, Folvite, thus enabling the Applicant to rely on the efficacy and safety findings of the LD.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed NDA 216395. The results of the bioequivalence studies conducted in this NDA submission establishes an adequate scientific bridge to Folvite and supports the approval of folic acid oral solution for the proposed indications at the doses approved for Folvite.

1.2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

- The results of the bioequivalence study 007-24 demonstrated that folic acid 1 mg/5ml oral solution under fasting conditions resulted in a relatively higher exposure of folic acid compared to the reference product. However, the higher bioavailability of folic acid under fasting conditions is not clinically significant. See section 2.2.3 for details.

- The results of the bioequivalence study 008-24 demonstrated that folic acid exposure between the 1 mg/5ml oral solution and the reference product under fed conditions is comparable. The marginally lower C_{max} of folic acid from the test product is not clinically significant. See section 2.2.4 for details.

2 QUESTION BASED REVIEW

This review is specific to the evaluation of clinical pharmacology studies included in the submission of NDA 216395, folic acid oral solution.

2.1 GENERAL ATTRIBUTES

2.1.1 What are general features of the drug product?

The Applicant has developed folic acid oral solution (1 mg/ 5 mL) intended to meet the needs of patients who require folic acid and have difficulty swallowing tablets. The recommended therapeutic dosage in adults (regardless of age) is up to 1 mg daily. Folic acid is a yellow or yellowish-orange, odorless, crystalline powder. Folic acid is very slightly soluble in water but readily dissolves in alkaline solutions.

2.1.2 What is the Applicant's rationale in developing this product?

The Sponsor is developing folic acid oral solution, 1 mg/5 ml as an alternative dosage form for the ease of administration to patients who, due to illness or age, have difficulty swallowing or may prefer a liquid formulation. Additionally, oral solution allows

physicians or patients to achieve appropriate age-dependent dose by allowing them to dose titrate by volume. This method is preferred over compounding/crushing tablets as it could lead to dosing inaccuracy and variability, impacting quality, safety and efficacy.

2.1.3 What is the proposed mechanism(s) of action of folic acid?

Folic acid is a precursor of tetrahydrofolic acid, which is a cofactor involved in the biosynthesis of purine and thymidylates of nucleic acids. Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective DNA synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias. Thus, folic acid acts on megaloblastic bone marrow to produce a normoblastic marrow.

What are the proposed therapeutic indication(s)?

In this 505(b)(2) NDA for folic acid oral solution, the Sponsor is seeking approval for the treatment for megaloblastic anemias due to a deficiency of folic acid in adults and pediatric patients. Folvite, the LD, is approved for the same indication.

2.1.4 What is the proposed dosing instruction for the listed drug?

The dosing instruction for the proposed product is similar to the LD and can be administered with or without food.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of clinical pharmacology studies used to support dosing or label claims?

In this submission, the Applicant submitted two clinical pharmacological studies intended to support a pharmacokinetic bridge with the reference standard. The two studies were oral comparative bioavailability studies between folic acid 1 mg/5 ml oral solution (Test product) and folic acid 1 mg tablet (Reference product) in healthy, adult, human subjects under fasting and fed conditions. The salient features of these studies include:

1. Comparator in the bioequivalence studies
   As stated earlier, Folvite (folic acid 1 mg tablets), the LD is not currently marketed. Even the reference listed drug (RLD) as per Orange Book folic acid 1 mg tablet by Watson Laboratories (ANDA # 080680) while not discontinued was not available for comparative purposes. The Agency recommended that the Applicant could use the ANDA product designated as the reference standard (RS) in the Orange Book to establish a bridge between the proposed drug product and the LD. Therefore, the Applicant used the Orange Book RS folic acid tablets, 1 mg, supplied by Amneal Pharmaceuticals (ANDA # 040625) as a comparator in the bioequivalence studies.

2. Low folate baseline concentrations
   The Applicant previously conducted (b) (4) and this study failed to meet the bioequivalence (BE) criteria (b) (4)

[redacted] This led the Applicant to suggest that prescreening the subjects for low serum folate concentration could help reduce variability. The Agency agreed and hence, both the bioequivalence studies conducted enrolled subjects with low folate concentrations. The study also limited the impact on folate plasma concentrations from concomitant medications, nutritional supplements, and food. Further, the Applicant used pre-dose folic acid levels for baseline adjustment of the post-dose levels. The Applicant also utilized a partial replicate crossover design to address the inherent pharmacokinetic variability.

3. Establishing bioequivalence on folic acid [redacted] the Agency recommended that bioequivalence should be established based on the parent drug (active ingredient), i.e., folic acid, as exposure of the parent drug is more sensitive to changes in drug formulation. The Agency mentioned that the Applicant could provide 5-MTHF data as supportive evidence.

2.2.2 Is the active moiety in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

A validated LC-MS/MS analytical method (MVR-23-130-FOL) for quantifying folic acid in human plasma treated with EDTA was used for the bioanalysis of PK samples in these studies. The internal standard is Folic Acid- $^{13}C_5$.

The bioanalytical validation summary is provided in Table 5.

Table 1: Bioanalytical Method Validation Summary for Folic acid Plasma Concentration Quantification

Validation Parameters	**Results Summary**
Linearity	$r \geq 0.9993$
Validated assay range (ng/mL)	0.100 to 60.025

<table>
<tr><td>Standard calibration concentrations (ng/mL)</td><td><table>
<tr><td>STD8</td><td>60.2</td></tr>
<tr><td>STD7</td><td>51.1</td></tr>
<tr><td>STD6</td><td>36.3</td></tr>
<tr><td>STD5</td><td>24.5</td></tr>
<tr><td>STD4</td><td>12.3</td></tr>
<tr><td>STD3</td><td>6.13</td></tr>
<tr><td>STD2</td><td>0.199</td></tr>
<tr><td>STD1</td><td>0.100</td></tr>
</table></td></tr>
<tr><td>QC concentrations (ng/mL) from stripped biological matrix</td><td><table>
<tr><td>HQC</td><td>48.0</td></tr>
<tr><td>MQC</td><td>24.0</td></tr>
<tr><td>M1QC</td><td>6.24</td></tr>
<tr><td>LQC</td><td>0.284</td></tr>
<tr><td>LLOQQC</td><td>0.101</td></tr>
</table></td></tr>
<tr><td>QC concentrations (ng/mL) from unstripped biological matrix</td><td><table>
<tr><td>HQC</td><td>48.1</td></tr>
<tr><td>MQC</td><td>24.1</td></tr>
<tr><td>M1QC</td><td>6.27</td></tr>
<tr><td>LQC</td><td>0.311</td></tr>
<tr><td>LLOQQC</td><td>0.128</td></tr>
</table></td></tr>
<tr><td>QC Intraday precision range (%) from stripped biological matrix</td><td>%CV (PA01): 2.43% to 10.19%</td></tr>
<tr><td>QC Intraday accuracy range (%) from stripped biological matrix</td><td>%Accuracy (PA01): 99.02% to 106.93%</td></tr>
<tr><td>QC Intraday precision range (%) from unstripped biological matrix</td><td>%CV (PA06): 1.37% to 10.57%</td></tr>
<tr><td>QC Intraday accuracy range (%) from</td><td>%Accuracy (PA06): 93.89% to 102.75%</td></tr>
</table>

unstripped biological matrix	
QC Interday precision range (%) from stripped biological matrix	%CV: 2.55% to 14.14%
QC Interday accuracy range (%) from stripped biological matrix	%Accuracy: 98.02% to 103.52%
QC Interday precision range (%) from unstripped biological matrix	%CV: 2.57% to 10.26%
QC Interday accuracy range (%) from unstripped biological matrix	%Accuracy: 90.68% to 102.06%
Average recovery (%) from stripped biological matrix	86.4 % for analyte 86.9% for ISTD
Average recovery (%) from unstripped biological matrix	81.7% for analyte 82.5 % for ISTD
Freeze-thaw stability (cycles) in stripped and unstripped plasma	Stable 5 cycles at -70°C ± 10°C
Short-Term Stability of Analyte in Matrix	Stable 12 hours at room temperature
Long term storage stability (days) in stripped plasma	189 Days @ -70 ± 10°C and 189 Days @ -20°C ±5°C
Long term storage stability (days) in unstripped plasma	191 Days @ -70 ± 10°C and 191 Days @ -20°C ±5°C
Selectivity in stripped and unstripped plasma	No interference was observed at retention time (RT) of the analyte (folic acid) in blank samples with less than 20% of analyte peak area of LLOQ samples. No interference was observed at RT of the internal standard (IS) (folic acid $^{13}C_5$) in blank samples and less than 5% of IS peak area of LLOQ blank samples is within all the 8 blank matrix lots.

<table>
<tr><td>Matrix Effect in stripped plasma</td><td>The matrix effect was minimal.<table><tr><td></td><td>HQC</td><td>LQC</td></tr><tr><td>Precision (%CV)</td><td>4.86</td><td>4.88</td></tr><tr><td>% Accuracy</td><td>98.39</td><td>100.1</td></tr></table></td></tr>
<tr><td>Matrix Effect in unstripped plasma</td><td>Endogenous folic acid levels were measured in different lots of plasma. Average endogenous folic acid concentration of 0.027 ng/ml was added to the nominal concentration to account for endogenous levels.<table><tr><td></td><td>HQC</td><td>LQC</td><td>LLOQ</td></tr><tr><td>% Accuracy</td><td>92.28% to 102.14%</td><td>84.54% to 98.81%</td><td>81.64% to 115.74%</td></tr></table></td></tr>
<tr><td>Potentially Interfering and Commonly Used Drugs</td><td>No interference at RT of the analyte and IS was observed.</td></tr>
<tr><td rowspan="3">Dilution integrity in unstripped plasma</td><td>2T</td><td>4T</td></tr>
<tr><td>% CV: 2.14</td><td>% CV: 1.58</td></tr>
<tr><td>% Accuracy: 102.3</td><td>% Accuracy: 110.9</td></tr>
<tr><td>Carryover in stripped plasma</td><td colspan="2">No carryover was observed at analyte and IS retention time.</td></tr>
</table>
Source: Method Validation Report

In summary, the bioanalytical method, as reported, appears to be validated and robust in supporting the results and conclusions from the bioequivalence study.

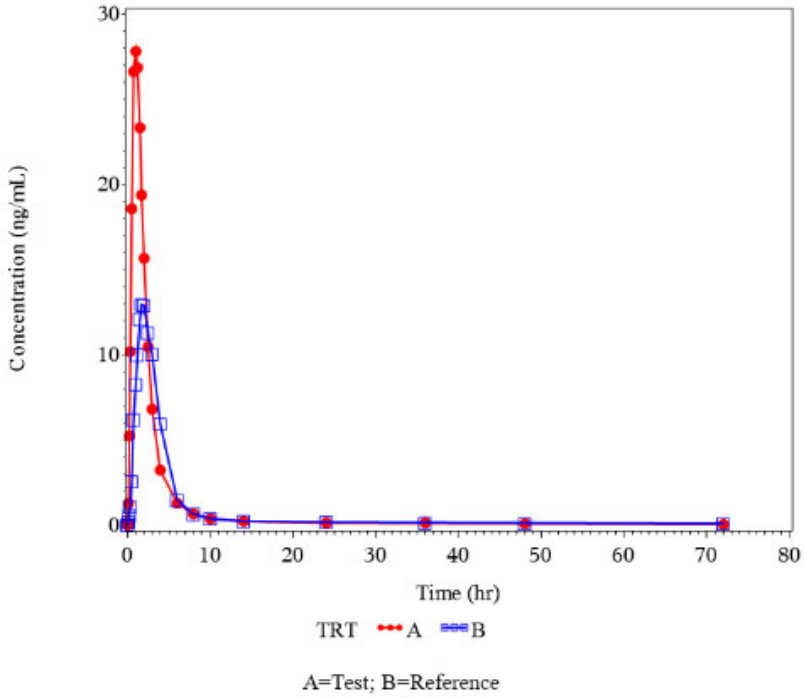
- OSIS clinical and analytical sites inspection:

  - The Office of Study Integrity and Surveillance (OSIS) determined that an inspection of both the clinical and analytical sites were not needed based on past inspections and their findings. See memo uploaded 5/29/2025 and 6/17/2025 under NDA 216395 in DARRTS.

2.2.3 What is the relative bioavailability of folic acid oral solution and folic acid tablet under fasting conditions?

To evaluate the relative bioavailability of folic acid 1mg/5ml oral solution and folic acid 1mg tablet under fasting conditions, the Applicant conducted a two treatment, three period, three sequence, partial replicate, crossover, single dose study. The results from this study demonstrated that both the rate and extent of absorption of folic acid from the test oral solution product was higher than the reference folic acid tablet as shown in Figure 1. As indicated in Table 2, under fasting conditions there was an increase in folic acid exposure, where C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ increased by 66.4%, 34.8% and 33%, respectively, for folic acid oral solution compared to the reference product.

Figure 1: Mean concentration-time profile of folic acid from reference (oral tablet) and test product (oral solution) under fasting conditions



Source: Reviewer's analysis

Table 2: Summary of average bioequivalence results of folic acid under fasting conditions

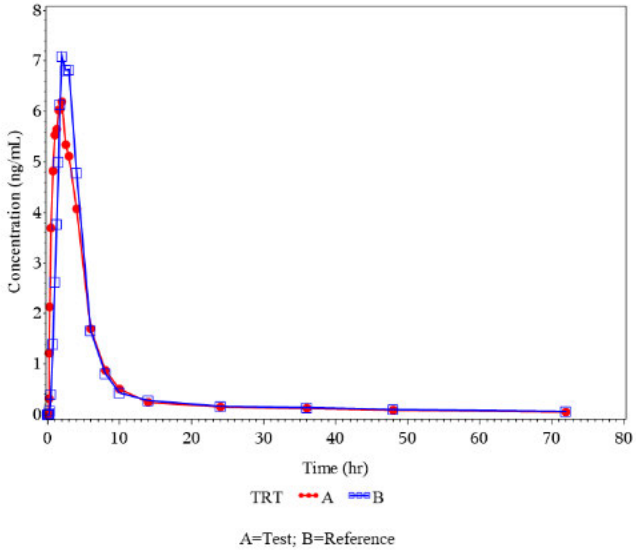
	Least Squares Geometric Means and Ratio of Means			90% Confidence Intervals	
Parameter (units)	Reference Product (R) (N=36)	Test Product (P) (N=35)	T/R	Lower 90% CI	Upper 90% CI
AUC_t (ng*hr/mL)	47.64	64.23	1.3482	122.67	148.18
AUC_i (ng*hr/mL)	49.55	65.88	1.3296	121.13	145.94
Cmax (ng/mL)	17.51	29.13	1.6641	149.62	185.07

Source: Reviewer's analysis

2.2.4 What is the impact of food on the bioavailability of folic acid from folic acid oral solution?

While the Applicant did not exactly conduct a food effect study for the folic acid oral solution, they compared the test and reference products under fed conditions following a two treatment, three period, three sequence, partial replicate, crossover, single dose study. A high fat high calorie breakfast having low folate diet was served 30 minutes prior to administration of both the test and reference products. As shown in Figure 2, the exposure of folic acid between the test and the reference product was comparable under fed conditions. Statistical analysis of the PK parameters in Table 3 shows that C_{max} of folic acid from the oral test solution was modestly lower (by 23.1%) than that of the reference product. However, both the AUC_t and AUC_i of the oral solution was comparable to the tablets. Additionally, cross study comparison (with the results of the fasting bioequivalence study) indicate that food likely has a negative impact on folic acid bioavailability since folic acid exposure was lower under fed conditions compared to fasting conditions for both test and reference product.

Figure 2: Mean concentration-time profile of folic acid from reference (oral tablet) and test (oral solution) product under fed conditions



Source: Reviewer's analysis

Table 3: Summary of average bioequivalence results of folic acid under fed conditions

	Least Squares Geometric Means and Ratio of Means			90% Confidence Intervals	
Parameter (units)	Reference product (R) (N=36)	Test Product (P) (N=35)	T/R	Lower 90% CI	Upper 90% CI
AUC_t (ng*hr/mL)	34.21	34.13	0.9977	92.11	108.06
AUC_i (ng*hr/mL)	36.09	35.48	0.9831	91.01	106.2
C_{max} (ng/mL)	8.91	6.86	0.7696	66.42	89.18

Source: Reviewer's analysis

2.2.5 Has a scientific bridge between folic acid oral solution and folic acid tablets been established by the Applicant?

The Sponsor conducted two comparative bioavailability studies to assess the exposure of folic acid between the oral solution and folic acid tablets. Under fasting conditions, the exposure of folic acid from the test oral solution product was greater than that of the reference folic acid tablets. However, this increase is not expected to be clinically significant due to the wide safety margin of folic acid. Excess folic acid not used by the body are typically excreted in urine. Folic acid has a short half-life, and the higher exposures will not lead to accumulation of folic acid upon repeat administration. Moreover, folic acid has been used in doses greater than the proposed dose of 1 mg with no serious safety concerns being reported. In the presence of food exposure to folic acid was similar between the test and the reference product. Therefore, in summary the Applicant has established an adequate scientific bridge for folic acid oral solution to the LD, Folvite (folic acid tablets).

3 APPENDIX INDIVIDUAL STUDY REVIEW

3.1 ORAL COMPARATIVE BIOAVAILABILITY STUDY FOR FOLIC ACID 1MG/5ML ORAL SOLUTION (FASTING)

Study No: 007-24	EDR link: \\CDSESUB1\EVSPROD\nda216395\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\007-24\fast-study-report-body.pdf

Title of study: Open label, balanced, randomized two-treatment, three-period, three sequence, partial replicate, single dose, crossover design to evaluate the oral comparative bioavailability of Folic acid from Folic acid 1 mg/5 ml oral solution (Test Product: CMP Development LLC, USA) with Folic acid 1 mg Tablets (Reference Product: Amneal Pharmaceuticals, USA) in healthy, adult, human subjects under fasting conditions.

Investigational product:
Test product: Folic acid 1 mg/5 ml oral solution
Reference: Folic acid 1 mg Tablets

Study:
Objectives:
To compare the oral comparative bioavailability of folic acid from the test product (T) with the reference product (R) after a single dose administration in healthy, adult human subjects under fasting conditions.

Study design: single center, phase 1, BE, open-label, randomized, single-dose, 3-period, 3-sequence, partial replicate crossover study.

- Treatment T: A single dose 5 mL (1mg) of Folic Acid Oral Solution 1 mg/5 ml (CMP Pharma) was administered into subject's mouth via syringe in a sitting posture with about 240 mL of drinking water.
- Treatment R: One tablet of Folic Acid 1mg (Amneal Pharmaceuticals Pvt. Ltd.) was administered orally to the subjects in a sitting posture with about 240 mL of water.

- Washout: 10 days
- Study participants: 38 healthy adults
- Sampling times (h): blood samples were collected prior to drug administration and 0.08, 0.17, 0.25, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 14.00, 24.00, 36.00, 48.00 and 72.00 hours post-dose.
- Pharmacokinetic parameters calculated:
  Primary parameters: Cmax, AUC0-t and AUC0-∞
  Secondary parameters: T_{max}, $AUC_{\_\%\ Extrap\_obs}$, $AUC_{\%ratio}$, $t_{1/2}$, and K_{el}

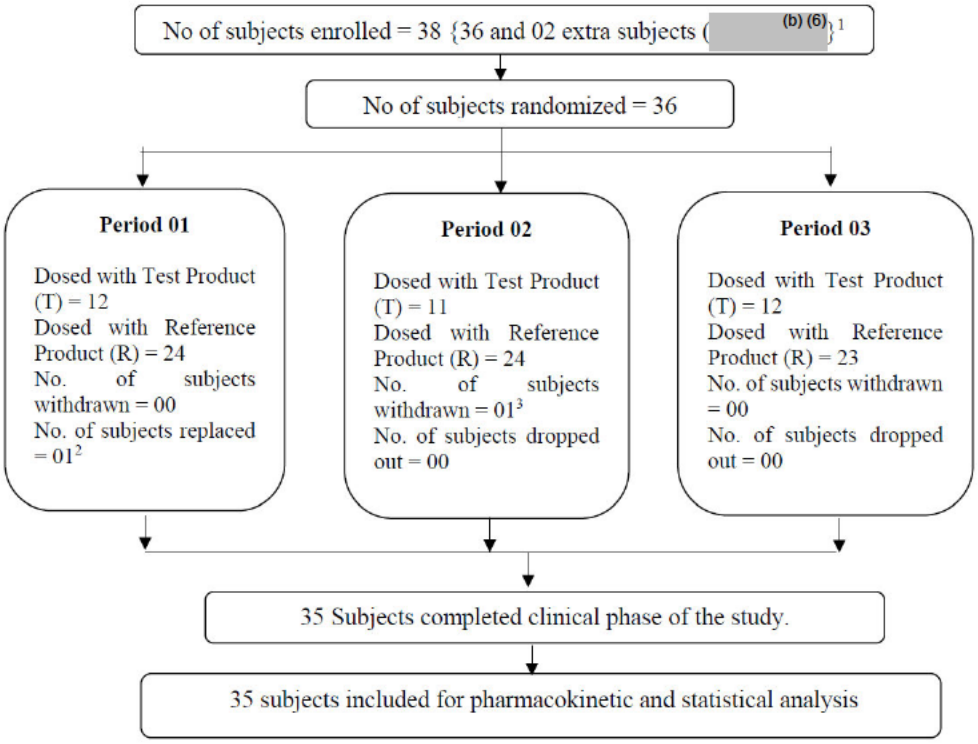
Analytical methods:
- A validated LC-MS method, as described in section 2.2.2, was used for quantification of folic acid in human plasma treated with K_2EDTA.
- The analytical range for folic acid in plasma was 0.100 to 60.025 ng/mL.
- Reviewer comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical methods:
- The statistical method for testing bioavailability was based on the determination of the 90% confidence interval around the ratio of the natural log (Ln)-transformed population means (Test/Reference) for the primary PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for baseline corrected folic acid.

- A mixed-scaling average bioequivalence approach was used for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for baseline corrected folic acid.
- If within-subject standard deviation of the reference formulation (SWR) is <0.294 for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ then using the two one-sided tests for bioequivalence, the test product is considered bioequivalent to the reference product, if the 90% confidence intervals for ratio (test/reference) of the geometric least square means of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the test and reference products is within acceptable bioequivalence limits of 80.00% to 125.00% based on Ln-transformed data.
- If within-subject standard deviation of the reference formulation (SWR) is ≥0.294 for primary pharmacokinetic parameters – C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ then test product is considered bioequivalent to the reference product, if the following two conditions are met for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ using Ln-transformed data:
  1. The 95% upper confidence bound for $(\mu T-\mu R)\ 2 - (\theta * S2WR)$ determined must be ≤ 0.
  2. The point estimate (test/reference geometric least mean ratio) must fall within acceptable bioequivalence limits of 80.00% to 125.00%.
- Employing the estimated plasma concentration-time profiles of baseline corrected folic acid PK parameters such as C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, T_{max}, $AUC_{\_\% Extrap\_obs}$, $AUC_{\%ratio}$, $t_{1/2}$, and Kel were calculated using SAS® (SAS Institute Inc., U.S.A.) version 9.4.
- Statistical analysis of the pharmacokinetic parameters was performed on PK parameters of baseline corrected folic acid using SAS® (SAS Institute Inc., U.S.A.) version 9.4.
- Consistent with mixed-scaling approach for bioequivalence, ANOVA was performed on Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for baseline corrected folic acid.

Results:
A total of 36 subjects were dosed in period 1 while 35 subjects were dosed in both period 2 and 3. A total of 35 subjects completed all the three periods of the study. Subject number (b) (6) withdrew consent and was replaced with subject number (b) (6). Subject number (b) (6) tested for alcohol during period 2 check-in and was withdrawn from the study.
The number of subjects included for pharmacokinetic and statistical analysis was 35. The flow chart indicated below describes the subject's disposition for the fasting study.

Figure 3: Subject's disposition flow chart



Source: Clinical Study Report Study 007-24, page 87 of 123.

For demographics information, see Table 4.

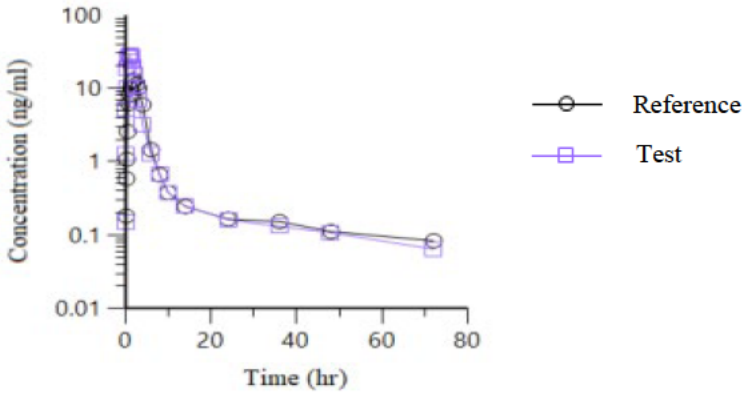
Table 4: Summary of demographic profile (N=35)

Variable		Profile		Percentage
Race		Asian		100.00%
		Others		0.00%
[redacted]		Male		48.57%
		Female		51.43%
Diet		Non-Vegetarian		100.00%
		Vegetarian		0.00%
Smoking status		Non-smokers		100.00%
		Smokers		0.00%
Alcohol Consumption		Non-alcoholics		100.00%
		Alcoholics		0.00%
	Mean	**SD**	**Min**	**Max**
Age (yrs)	32.1	4.27	23	41
Height (cm)	159.4	8.22	143	177
Weight (Kg)	58.334	6.0223	50.60	68.50
BMI (Kg/m^2)	22.946	1.5685	19.15	24.74

Source: Clinical Study Report Study 007-24, page 92 of 123.

For plasma concentration time profiles, and bioequivalence analysis results, see Figure 4 and Table 2. The within-subject standard deviation of the reference formulation (SWR) was ≥0.294 only for C_{max}. While a scaled average bioequivalence approach was employed for the comparison of C_{max} (Table 5), it still failed to meet the bioequivalence criteria.

Figure 4: Semilog plot of mean concentration-time profile of folic acid from reference (oral tablets) and test (oral solution) product under fasting conditions



Source: Reviewer's analysis

Table 5: Summary of scaled average bioequivalence results of folic acid under fasting conditions

Parameter	T/R Ratio	s2wr	sWR	N (sWR)	Criteria Bound	N (TR)	Method Used
AUC_t	1.3468	0.0448126	0.21169	35	0.1190113	35	Unscaled
AUC_i	1.3278	0.0398321	0.1995799	35	0.1109991	35	Unscaled
C_{max}	1.6652	0.0907276	0.3012102	35	0.3127058	35	Scaled/PE

Source: Reviewer's analysis

Conclusion:
The least square geometric means ratios (T/R) and 90% C.I. of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were respectively 166.41% (149.62% - 185.07%), 134.82% (122.67% - 148.18%), and 132.96% (121.13% - 145.94%).
Based on the statistical analysis of the comparative bioavailability of the Ln-transformed primary PK parameters (C_{max}, AUC_{0-t} and AUC0-∞) for baseline-corrected folic acid, the geometric least squares mean T/R ratio (%) of the test product (T) and reference product (R) were observed to be greater than 125.00% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Thus, the test product demonstrated a significantly higher comparative bioavailability than the reference product.

3.2 ORAL COMPARATIVE BIOAVAILABILITY STUDY FOR FOLIC ACID 1MG/5ML ORAL SOLUTION (FED)

Study No: 008-24	EDR link: \\CDSESUB1\evsprod\NDA216395\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\008-24\fed-study-report-body.pdf

Title of study: 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: CMP Development LLC, USA) and Folic acid 1 mg Tablet (Reference Product: Amneal Pharmaceuticals, USA in healthy, adult, human subjects under fed condition.

Investigational product:
Test product: Folic acid 1 mg/5 ml oral solution
Reference: Folic acid 1 mg Tablets

Study:
Objectives:
To compare the oral comparative bioavailability of folic acid from the test product (T) with the reference product (R) after a single dose administration in healthy, adult human subjects under fed conditions.

Study design: single center, phase 1, BE, open-label, randomized, single-dose, 3-period, 3-sequence, partial replicate crossover study.

- Treatment T: After an overnight fast of at least 10.00 hours, a high fat high calorie breakfast having low folate diet was served 30 minutes prior to administration of investigational products. All subjects consumed whole breakfast within 30 minutes of it being served. Exactly 30 minutes after actual start time of a high fat high calorie breakfast having low folate diet, a single dose 5 mL (1 mg) of folic Acid Oral Solution 1 mg/5 ml was administered into subject's mouth via syringe in a sitting posture with about 240 mL of drinking water.
- Treatment R: After an overnight fast of 10.00 hours, a high fat high calorie breakfast having low folate diet was served 30 minutes prior to administration of Investigational products. All subjects consumed whole breakfast within 30 minutes of it being served. Exactly 30 minutes after actual start time of a high fat high calorie breakfast having low folate diet, one tablet of folic Acid 1mg was administered orally to the subjects in a sitting posture with about 240 mL of water.

- Washout: 10 days
- Study participants: 37 healthy adults
- Sampling times (h): blood samples were collected prior to drug administration and 0.08, 0.17, 0.25, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 14.00, 24.00, 36.00, 48.00 and 72.00 hours post-dose.
- Pharmacokinetic parameters calculated:
  Primary parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$
  Secondary parameters: T_{max}, $AUC_{\_\% Extrap\_obs}$, $AUC_{\%ratio}$, $t_{1/2}$, and K_{el}

Analytical methods:
- A validated LC-MS method, as described in section 2.2.2, was used for quantification of folic acid in human plasma treated with K_2EDTA.
- The analytical range for folic acid in plasma was 0.100 to 60.025 ng/mL.
- Reviewer comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical methods:
- The statistical method for testing bioavailability was based on the determination of the 90% confidence interval around the ratio of the natural log (Ln)-transformed population means

(Test/Reference) for the primary PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for baseline corrected folic acid.

- A mixed-scaling average bioequivalence approach was used for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for baseline corrected folic acid.
- If within-subject standard deviation of the reference formulation (SWR) is <0.294 for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ then using the two one-sided tests for bioequivalence, the test product is considered bioequivalent to the reference product, if the 90% confidence intervals for ratio (test/reference) of the geometric least square means of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the test and reference products is within acceptable bioequivalence limits of 80.00% to 125.00% based on Ln-transformed data.
- If within-subject standard deviation of the reference formulation (SWR) is ≥0.294 for primary pharmacokinetic parameters – C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ then test product is considered bioequivalent to the reference product, if the following two conditions are met for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ using Ln-transformed data:
  1. The 95% upper confidence bound for (μT-μR) 2 – (θ*S2WR) determined must be ≤ 0.
  2. The point estimate (test/reference geometric least mean ratio) must fall within acceptable bioequivalence limits of 80.00% to 125.00%.
- Employing the estimated plasma concentration-time profiles of baseline corrected folic acid PK parameters such as C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, T_{max}, $AUC_{\_\%\ Extrap\_obs}$, $AUC_{\%ratio}$, $t_{1/2}$, and Kel were calculated using SAS® (SAS Institute Inc., U.S.A.) version 9.4.
- Statistical analysis of the pharmacokinetic parameters was performed on PK parameters of baseline corrected folic acid using SAS® (SAS Institute Inc., U.S.A.) version 9.4.
- Consistent with mixed-scaling approach for bioequivalence, ANOVA was performed on Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for baseline corrected folic acid.

Results:

A total of 37 healthy, adult, human subjects were enrolled in the study. 36 subjects were dosed in period 01, 35 subjects were dosed in period 02 and 34 subjects were dosed in period 03. Out of 36 subjects, 34 subjects completed all the three periods of the study. Subject number (b) (6) withdrew consent prior to period 01 dosing and was replaced with subject number (b) (6). Subject number (b) (6) tested for alcohol during period 02 check-in and was withdrawn from the study.

For demographics information, see Table 5

Table 6: Summary of demographic profile (N=34)

Variable		Profile		Percentage
Race		Asian		100.00%
		Others		0.00%
[redacted]		Male		47.06%
		Female		52.94%
Diet		Non-Vegetarian		100.00%
		Vegetarian		0.00%
Smoking status		Non-smokers		100.00%
		Smokers		0.00%
Alcohol Consumption		Non-alcoholics		100.00%
		Alcoholics		0.00%
	Mean	SD	Min	Max
Age (yrs)	29.6	6.33	19	41
Height (cm)	158.3	8.20	146	176
Weight (Kg)	57.762	5.5637	50.50	71.80
BMI (Kg/m^2)	23.070	1.7416	19.15	24.65

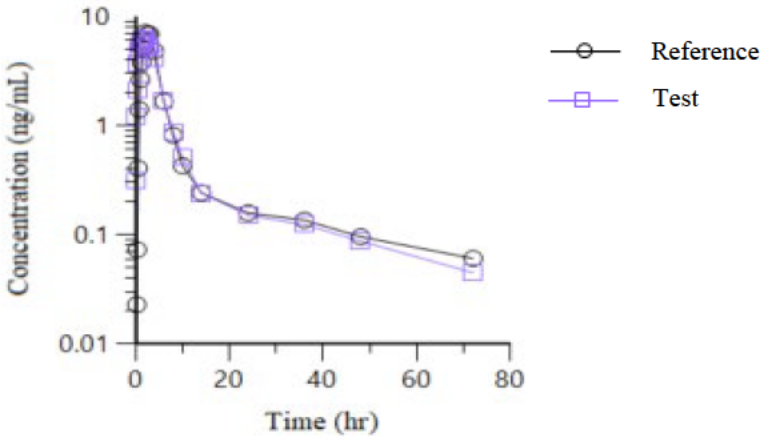
Source: Clinical Study Report Study 008-24, page 93 of 127.

The folic acid plasma concentration for the reference product for subject number 25 increased significantly at 10, 14 and 24 hours and appeared as outliers. This resulted in an unusual spike for the plasma concentration-time profile of the reference product. Due to this a sensitivity analysis was conducted to assess the impact of these outliers. For the sensitivity analysis the concentrations of subject

number 25 at 10, 14 and 24 hours were substituted with the mean concentration of the remaining subjects at the same timepoints being administered the reference tablet. Upon re-analysis, the plasma concentration time profile of folic acid was comparable between the reference and test product for all time points.

For plasma concentration time profiles, and bioequivalence analysis results, see Figure 5, and Table 3. The within-subject standard deviation of the reference formulation (SWR) was ≥0.294 only for C_{max}. While a scaled average bioequivalence approach was employed for the comparison of C_{max} (Table 7), it still failed to meet the bioequivalence criteria.

Figure 5: Semilog plot of mean concentration-time profile of folic acid from reference (oral tablets) and test (oral solution) product under fed conditions



Source: Reviewer's analysis

Table 7: Summary of scaled average bioequivalence results of folic acid under fed conditions

Parameter	T/R Ratio	s2wr	sWR	N (sWR)	Criteria Bound	N (TR)	Method Used
AUC_t	1.0083	0.043407	0.2083434	34	-0.021891	34	Unscaled
AUC_i	0.9924	0.037023	0.1924135	34	-0.018208	34	Unscaled
C_{max}	0.7776	0.2006122	0.4478975	34	0.0126939	34	Scaled/PE

Source: Reviewer's analysis

Conclusion:
The least square geometric means ratios (T/R) and 90% C.I. of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were respectively 76.96% (66.42% - 89.18%), 99.77% (92.11% - 108.06%), and 98.31% (91.01% - 106.2%).

Based on the statistical analysis of the comparative bioavailability of the Ln-transformed primary PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) for baseline-corrected folic acid, the geometric least squares mean T/R ratio (%) of the test product (T) and reference product (R) was observed to be less than 80.0% for C_{max}. However, for AUC_{0-t} and $AUC_{0-\infty}$ the T/R ratio (%) was within 80.0% to 125.0%. Thus, the moderate decrease in the C_{max} of folic acid from the test product under fed conditions does not suggest a meaningful clinical impact as the overall exposure of folic acid is comparable between the test and the reference product.

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/s/

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