Method Pharmaceuticals

Date: January 11, 2024

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
Room 1061, l-IFA-305
5630 Fishers Lane
Rockville, MD 20852

ANDA Suitability Petition for Folic Acid, Oral Solution

Dear Sir or Madam,

Method Pharmaceuticals, LLC., submits this ANDA Suitability Petition pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FDC Act), and in accordance with 21 C.F.R. § 10.20, § 10.30 and § 314.93. The Suitability Petition requests the FDA to confirm that Folic Acid Oral Solution, 0.1 mg/mL, and 1 mg/mL is suitable for submission in an Abbreviated New Drug Application (ANDA).

A. Action Requested:

The Suitability Petition requests that the FDA determine that the proposed Folic Acid Oral Solution, 0.1 mg/mL and 1 mg/mL is suitable for submission in an ANDA. This Suitability Petition pursuant to Section 505(j)(2)(C) of the FDC Act and 21C.F.R. §314.93, is the appropriate mechanism for securing FDA authorization to submit an ANDA for a drug product that differs in dosage form from the Reference Listed Drug (RLD).

The Reference Listed Drug (RLD) upon which this petition based is

- Folic Acid Tablets, 1 mg which FDA approved prior to January 1, 1982, under ANDA A080680 as identified in the Orange Book.

The relevant copies of the pages from the current Electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for Folic Acid Tablets, 1 mg, are provided as ***Attachment 1***.

The drug, the route of administration and the recommendations for use are the same as the reference listed drug product. The proposed drug product would differ only in dosage form from marketed tablet products.

Approval of this Suitability Petition would allow Method Pharmaceuticals LLC., to submit Folic Acid Oral Solution, 0.1 mg/mL and 1 mg/mL as an ANDA, and would permit convenient dosing and administration by healthcare providers to treat patients with 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 in accordance with the approved indications for Folic Acid Tablets.

B. Statement of Grounds:

The FDC Act permits, at Section 505(j)(2)(A)(iii) and 21C.F.R. §314.93, the submission of an ANDA for a drug product that differs in dosage form from the RLD after FDA has approved a petition seeking permission to file such an application.

Folic Acid Tablets, 1 mg which FDA approved prior to January 1, 1982, under ANDA A080680 as identified in the Orange Book.

Reference is also made to the official USP monograph for "Folic Acid Compounded Oral Solution, 1 mg/mL" (***attachment 2***)

Based on the above referenced ANDA, proven safety, and efficacy studies (where required) and subsequent approval of the ANDA, it is our understanding that the 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 with Folic Acid Oral Solution, 0.1 mg/mL and 1 mg/mL would be safe and efficacious. A copy of the most recent labeling for the FDA designated Reference Standard (***attachment 3***) approved under ANDA A040625 (since the current RLD label is not available), revised May 2018 is provided as ***Attachment 4.***

Method Pharmaceuticals LLC., proposes Folic Acid Oral Solution, 0.1 mg/mL and 1 mg/mL administered for the approved indication same as the Folid Acid Tablets. The following table 1 presents the comparison between the approved and proposed drug product strengths:

Table 1: Comparison of Approved Drug Product to Proposed Drug Product

Product Name as approved and as listed in the Orange Book (Reference Listed Drug)	Dosage Form	Route of Administration	Proposed Strengths of Folic Acid Oral Solution for Our ANDA	Proposed Dosage Form
Folic Acid Tablets, 1 mg approved under ANDA A080680	Tablets	Oral	0.1 mg/mL 1 mg/mL	Oral Solution

Approved Indications and Usage:

Folic acid 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.

ANDA Suitability Petition
Folic Acid Oral Solution, 0.1 mg/mL, and 1 mg/mL

Approved Dosage and Administration:

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 B12 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 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.

Proposed Indications and Usage:

The proposed Folic Acid Oral Solution 0.1 mg/mL and 1 mg/mL is consistent with the RLD labeling in all respects as applicable to Folic Acid Tablets indications.

Additionally, because only 1 mg strength in tablet dosage form is currently approved, the dose adjustment can be done by splitting/grinding the tablet. Please note that the approved Folic Acid Tablets are scored and therefore, may poses difficulty to administer lower dose below 0.5 mg. Introduction of an oral dosage form with 0.1 mg/mL additional strength in solution dosage form will allow additional flexibility to set the dose for the maintenance level dosage regimen. An example dosage regimen for the maintenance level dosage recommendations consistent with the approved dosage administration is presented in table 2 below.

Table 2: Dosage regimen based on patient's age and type.

Patients Age/ Type	Approved Dosage for Maintenance Level	Prescribed Minimum Dose in mL (0.1 mg/mL)
Infants	0.1 mg	1 mL
Children under 4 years of age	0.3 mg	3 mL
Adults and children 4 or more years of age	0.4 mg	4 mL
Pregnant and lactating women	0.8 mg	8 mL

ANDA Suitability Petition
Folic Acid Oral Solution, 0.1 mg/mL, and 1 mg/mL

Method Pharmaceuticals LLC., believes that the pediatric assessment is not applicable to the proposed Folic Acid Oral Solution, drug product, because the proposed change concerns only facilitates the availability of the drug product in solution dosage form in place of a tablet dosage, with the active ingredient, indication, route of administration and dosing regimen remains identical to that for Folic Acid Tablets, 1 mg as approved under ANDA A080680 ***(Attachment 4).*** Therefore, Method Pharmaceuticals LLC., does not plan to submit any pediatric assessments with its application.

Additionally, Folic Acid Tablets, 1 mg is designated with "AA" rating in the current Electronic Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) and the proposed drug product is a solution dosage form. Therefore, Method Pharmaceuticals LLC., does not plan to submit any bioequivalence protocol to the Office of Generic Drugs, Division of Bioequivalence under Section 505(j) (2) (A) (iv) of the Act.

Method Pharmaceuticals LLC., proposed Folic Acid Oral Solution does not pose questions of Safety or Effectiveness since the proposed strengths are the recommended product doses stated in the approved labeling of the referenced listed drug approved under ANDA A080680. The active ingredient, dosage regimen, uses and route of administration of the proposed strengths are /will be the same as applicable to the Folic Acid Tablets as approved under the referenced ANDA A080680.

Draft labeling for the proposed Folic Acid Oral Solution, 0.1 mg/mL and 1 mg/mL is provided as ***Attachment 5.***

As summarized above, Method Pharmaceuticals LLC., requests the FDA to confirm the proposed Folic Acid Oral Solution, 0.1 mg/mL and 1 mg/mL drug product is suitable for submission as an ANDA.

C. Environmental Impact:

Method Pharmaceuticals LLC., claims a categorical exclusion under 21 C.F.R. § 25.31.

D. Economic Impact Statement:

Method Pharmaceuticals LLC., does not believe that this requirement is applicable at this time, but will agree to submit economic impact information, in accordance with 21 C.F.R. § 10.30(b), if requested by the Agency.

E. Certification:

Method Pharmaceuticals LLC., certifies that to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

ANDA Suitability Petition
Folic Acid Oral Solution, 0.1 mg/mL, and 1 mg/mL

Enclosures:

Attachment 1: Approved Drug Products with Therapeutic Equivalence Evaluations, accessed December 21, 2023 (Orange Book) - RLD

Attachment 2: USP monograph for "Folic Acid Compounded Oral Solution, 1 mg/mL."

Attachment 3: Approved Drug Products with Therapeutic Equivalence Evaluations, accessed December 21, 2023 (Orange Book) - RS

Attachment 4: Package Insert Labeling for Reference Standard, ANDA 040625 for Folic Acid Tablets USP, 1 mg.

Attachment 5: Draft Package Insert Labeling for Folic Acid Oral Solution, 0.1 mg/mL, and 1 mg/mL.

Sincerely,
For Method Pharmaceuticals LLC.

Scott Tucker
Chief Executive Officer