



Suggested Formula	Folic Acid 5 mg/mL Intravenous Injection (Solution, 10 mL)	FIN	F 003 199v3
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SUGGESTED FORMULATION

Ingredient Listing	Qty.	Unit	NDC #	Supplier	Lot Number	Expiry Date
Folic Acid, USP	TBD					
Ascorbic Acid, USP	0.01	g				
Methylparaben, NF	0.02	g				
Sodium Chloride, USP	0.04	g				
Propylene Glycol, USP	0.1	mL				
Sterile Water for Injection, USP	9.0	mL				
Sterile Water for Injection, USP	q.s. to 10.0	mL				
Sodium Hydroxide 1N Solution	As required					

SPECIAL PREPARATORY CONSIDERATIONS

Ingredient-Specific Information

- Plastic Reactive / Adsorbent** (do not allow to come into contact) *Methylparaben*
- Light Sensitive** (protect from light whenever possible): *Folic Acid, Propylene Glycol, Ascorbic Acid*
- Hygroscopic** (protect from moisture whenever possible): *Propylene Glycol*
- Oxygen Sensitive** (protect from air whenever possible): *Ascorbic Acid*



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SPECIAL PREPARATORY CONSIDERATIONS (CONTINUED)

Suggested Preparatory Guidelines

Non-Sterile Preparation Sterile Preparation

Processing Error / Testing Considerations: To account for processing error, pH adjustment, sterility and endotoxin testing considerations during preparation, it is suggested to measure an additional **20% to 25%** of the required quantities of ingredients.

Special Instruction: This formula may contain one or more Active Pharmaceutical Ingredients (APIs) that may be classified as hazardous, please refer & verify the current NIOSH list of Antineoplastic and Other Hazardous Drugs in Healthcare Settings. At this time, **General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings** is informational and not compendially applicable unless otherwise specified by regulators and enforcement bodies. For information on the scope, intended applicability, and implementation context for USP General Chapter <800>, see: <https://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare>.

This formula must be prepared within the appropriate facilities under adequate environmental conditions, following the necessary guidelines and procedures as stated within *USP 797* and *USP 800* when handling hazardous drugs. Only trained and qualified personnel must prepare this formula.

All heat stable, reusable materials and equipment must be sterilized and depyrogenated by dry heat sterilization at 250°C for 2 hours prior to use.

Compounder needs to verify as per USP, if every batch of final product compounded using this procedure must be sterility and endotoxin tested before being dispensed.

All required personal protective equipment (sterile and hazardous if applicable), such as but not limited to, gowns, aprons, sleeves, gloves both inner and outer if applicable, shoe covers, hairnet, head cap, beard cover, eyewear, appropriate face mask, respirator and face shield, etc., where applicable must be worn at all times. In addition, proper personnel cleansing must be done before entering the buffer or clean area.

If applicable, follow all required procedures for hazardous drug handling including but not limited to procurement, transport, storage, preparation, dispensing, administration, clean up (spills) & disposal.

Filter integrity must be validated by performing a filter stress test. If the test demonstrates that the filter might be defective, the solution must be discarded and remade.

If you are a registered 503B facility, please refer to all relevant guidance documents including but not limited to the Code of Federal Regulations (CFR), Guidance for Industry (GFI) and Compliance Policy Guides (CPGs).

This procedure requires the use of very small quantities of ingredients. All calculations and preparation techniques must be verified before dispensing the final product.



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SUGGESTED PREPARATION (for 10 mL)

Weigh and / or measure the following ingredients when appropriate:

Ingredient Listing	Qty.	Unit	Multiplication factor (*): _____	Processing Error	Qty. to measure
Folic Acid, USP §	TBD				
Ascorbic Acid, USP §	0.01	g			
Methylparaben, NF §	0.02	g			
Sodium Chloride, USP §	0.04	g			
Propylene Glycol, USP §	0.1	mL			
Sterile Water for Injection, USP §	9.0	mL			
Sterile Water for Injection, USP §	q.s. to 10.0	mL			
Sodium Hydroxide 10% Solution §	As required				

* Takes into account increased batch size conversions and density conversions, if required.

§ Weigh / measure just prior to use.

Preparatory Instruction

IMPORTANT: All preparatory procedures must be performed using proper Aseptic Technique

1. **Equipment sterilization:**

Following the manufacturer's specifications, sterilize and depyrogenate all heat stable, reusable materials and equipment, then return to ambient temperature.



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2. **Ingredient quantification:**

A. Determine the potency of Folic Acid based on the certificate of analysis:

MINUS	100%
Water Content (from certificate of analysis)	_____ %
DIVIDED BY	100
EQUALS	
Quantity of water free Folic Acid, in decimal	_____
MULTIPLIED BY	
Assay on anhydrous basis result (from certificate of analysis)	_____ %
DIVIDED BY	100
EQUALS	
i. Potency of Folic Acid, in decimal	_____



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3.	<p><u>Ingredient quantification:</u></p> <p>A. Determine the quantity (in g) of Folic Acid required to make a Folic Acid 5 mg/mL Intravenous Injection, batch size (10 mL):</p> <table border="1" style="width: 100%;"><tr><td>Quantity of Folic Acid needed for 10 mL</td><td style="text-align: right;">0.050 g</td></tr><tr><td colspan="2">DIVIDED BY</td></tr><tr><td>Potency of Folic Acid, in decimal (Step 2Ai)</td><td style="text-align: right;">_____</td></tr><tr><td colspan="2">EQUALS</td></tr><tr><td>i. Actual Quantity of Folic Acid needed for 10 mL</td><td style="text-align: right;">_____ g</td></tr><tr><td colspan="2">MULTIPLIED BY</td></tr><tr><td>Processing error adjustments (20 to 25%)</td><td style="text-align: right;">1.20 to 1.25</td></tr><tr><td colspan="2">EQUALS</td></tr><tr><td>ii. Quantity of Folic Acid needed <i>plus</i> processing error adjustments</td><td style="text-align: right;">_____ g</td></tr></table>	Quantity of Folic Acid needed for 10 mL	0.050 g	DIVIDED BY		Potency of Folic Acid, in decimal (Step 2Ai)	_____	EQUALS		i. Actual Quantity of Folic Acid needed for 10 mL	_____ g	MULTIPLIED BY		Processing error adjustments (20 to 25%)	1.20 to 1.25	EQUALS		ii. Quantity of Folic Acid needed <i>plus</i> processing error adjustments	_____ g
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EQUALS																			
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4.	<p><u>Powder preparations:</u></p> <p>A. Combine and triturate the following ingredients together to form a fine, homogeneous powder blend:</p> <ul style="list-style-type: none">-Folic Acid (amount determined in Step 3Aii)-Ascorbic Acid-Sodium Chloride																		
5.	<p><u>Liquid preparation:</u></p> <p>A. Combine and mix the following ingredients together:</p> <ul style="list-style-type: none">-Methylparaben-Propylene Glycol <p><u>End result:</u> Homogeneous liquid-like solution.</p>																		



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6.	<p><u>Powder-Liquid integration:</u></p> <p>A. In the given order, sequentially add the following ingredients to the Sterile Water for Injection (9.0 mL <i>plus</i> processing error adjustments):</p> <ul style="list-style-type: none">-Homogeneous liquid-like solution (Step 5A)-Fine, homogeneous powder blend (Step 4A) <p><u>Specifications:</u> Continuously mix.</p> <p><u>End result:</u> Homogeneous liquid-like dispersion.</p> <p><u>Note:</u> Add the next ingredient, once the previous one has been completely added and dispersed.</p>
7.	<p><u>pH testing:</u></p> <p>A. Draw an appropriate amount of the mixture (Step 6A).</p> <p>B. Test the pH of the sample. It should lie between 8.0 and 9.0.</p> <p>C. <u>If the pH < 8.0, carefully add, in a dropwise fashion, the Sodium Hydroxide 10% Solution to the mixture:</u></p> <ol style="list-style-type: none">1. Draw and transfer 1 or 2 drops of the Sodium Hydroxide 10% Solution to the mixture.2. Stir for at least 5 minutes to evenly disperse the Sodium Hydroxide 10% Solution.3. Re-test the pH.4. Continue to add the Sodium Hydroxide 10% Solution until the pH of 8.0 to 9.0 is obtained. <p>IMPORTANT: Do not allow the pH to rise above 9.0.</p>
8.	<p><u>Filling to volume:</u></p> <p>A. Add additional Sterile Water for Injection to the above mixture to fill to the required batch size (10.0 mL <i>plus</i> processing error adjustments).</p> <p><u>Specifications:</u> Continuously mix.</p> <p><u>End result:</u> Homogeneous liquid-like solution.</p>
9.	<p><u>Filtering and transferring:</u></p> <p>Aseptically filter the solution through a 0.22-μm sterile filter into the recommended dispensing container (see Packaging requirements). Transfer the remainder into a separate dispensing container. This is to be used as the Test sample for sterility and endotoxin testing.</p>



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10.	<p><u>Filter integrity test:</u></p> <p>Validate filter integrity by performing a filter stress test. If the test demonstrates that the filter might be defective, the solution must be discarded and remade.</p>
11.	<p><u>Terminal Sterilization:</u></p> <p>In relation to the chemical composition of the formulation, final packaging, etc., select and validate an end-stage sterilization method and follow the manufacturer's specifications.</p>
12.	<p><u>Sterility and Endotoxin testing:</u></p> <p>Validate the Test sample for sterility and endotoxins, in accordance to current USP 797 regulatory guidelines.</p>

SUGGESTED PRESENTATION

Estimated Beyond-Use Date	24 hours controlled room temperature, 3 days refrigerated, or 45 days frozen, as per USP 797. BUD based on successful endotoxin test result.	Packaging Requirements	Sterile, tightly closed, light-resistant unit-dose injection vials.
Auxiliary Labels	1 Use as directed. Do not exceed prescribed dose.	5	Discard container after use.
	2 Keep out of reach of children.	6	Discard in the presence of particulate matter.
	3 Protect from light.	7	Do not use if discolored.
	4 Consult your health care practitioner if any other prescription or over-the-counter medications are currently being used or are prescribed for future use.	8	Keep at controlled room temperature (20°C – 25°C), refrigerated (2°C – 8°C) or frozen (-25°C to -10°C).
Pharmacist Instructions	Add any auxiliary labels specific to the API to the dispensing container as deemed necessary.		
Patient Instructions	Contact your pharmacist in the event of adverse reactions.		



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REFERENCES

1.	USP <797> Pharmaceutical Compounding – Sterile Preparations. US Pharmacopeial Convention, Inc. <i>United States Pharmacopeia XXVIII / National Formulary 23</i> . Rockville, MD. 2004: 2461.
2.	Methylparaben. In: Rowe RC. <i>Handbook of Pharmaceutical Excipients, 4th Edition</i> . American Pharmaceutical Association; 2003: 390.
3.	Ascorbic Acid. In: Rowe RC. <i>Handbook of Pharmaceutical Excipients, 4th Edition</i> . American Pharmaceutical Association; 2003: 32.
4.	Folic Acid (Monograph). In: O'Neil MJ. <i>The Merck Index 14th Edition</i> . Whitehouse Station, NJ: Merck & Co, Inc.; 2006: Monograph #4221.
5.	Chapter 8: Buffered and Isotonic Solutions. In: Martin, A. <i>Physical Pharmacy, Fourth Edition</i> . Philadelphia, PA: Lippincott Williams & Wilkins; 1993: 169~189.
6.	Folic Acid. In: Trissel LA. <i>Trissel's Stability of Compounded Formulations, 2nd Edition</i> . American Pharmaceutical Association; 2000: 164.
7.	Folic Acid (Monograph). <i>United States Pharmacopeia XXVIII / National Formulary 23</i> . Rockville, MD. US Pharmacopeial Convention, Inc. 2004: 869.

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