MEDISCA® NETWORK INC.
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Suggested Formula	Methotrexate 25 mg/mL Intramuscular Injection (Solution, 10 mL)	FIN	F 004 923v2

SUGGESTED FORMULATION

Ingredient Listing	Qty.	Unit	NDC #	Supplier	Lot No.	Expiry Date
Methotrexate, USP	TBD					
Benzyl Alcohol, NF	0.2	mL				
Sodium Chloride, USP	0.036	g				
Sterile Water For Injection, USP	8.0	mL				
Sterile Water For Injection, USP	q.s. to 10.0	mL				
Sodium Hydroxide 10% Solution	As required					
Hydrochloric Acid 10% Solution	As required					

SPECIAL PREPARATORY CONSIDERATIONS

Ingredient-Specific Information

Light sensitive *(protect from light whenever possible):* *Methotrexate, Benzyl Alcohol*

Hygroscopic *(protect from moisture whenever possible):* *Methotrexate*

Suggested Preparatory Guidelines

☐ Non-Sterile Preparation ■ Sterile Preparation

Processing Error / Testing Considerations: To account for processing error, pH testing, sterility and endotoxin testing considerations during preparation, it is suggested to measure an additional **15 to 20%** of the required quantities of ingredients.

Special Instruction: This formula must be prepared within the appropriate facilities under adequate environmental conditions, following the necessary guidelines and procedures as stated within *USP 797*. 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.

Every batch of final product compounded using this procedure must be sterility and endotoxin tested before being dispensed.

Protective apparel, such as a sterile gown, sterile gloves, shoe covers, head cap, eyewear and face-masks should always be worn. In addition, proper personnel cleansing must be done before entering the buffer or clean area.

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.

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
Methotrexate, USP §	TBD				
Benzyl Alcohol, NF §	0.2	mL			
Sodium Chloride, USP §	0.036	g			
Sterile Water For Injection, USP §	8.0	mL			
Sterile Water For Injection, USP §	q.s. to 10.0	mL			
Sodium Hydroxide 10% Solution §	As required				
Hydrochloric Acid 10% Solution §	As required				

* Takes into account increased batch size conversions and density conversions, if required.
§ Weigh / measure just prior to use.

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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.

2. **Ingredient quantification:**

   A. Determine the potency of Methotrexate based on the certificate of analysis:

	100%
MINUS	
Water Content (from certificate of analysis)	_____ %
DIVIDED BY	100
EQUALS	
Quantity of Methotrexate remaining after drying, in decimal	_____
MULTIPLY BY	
Assay on dried basis result (from certificate of analysis)	_____ %
DIVIDED BY	100
EQUALS	
i. Potency of Methotrexate, in decimal	_____

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3. **Ingredient quantification:**

A. Determine the quantity (in g) of Methotrexate required to make a 10 mL batch of Methotrexate 25 mg/mL Injection:

Quantity of Methotrexate required for 10 mL Injection	0.250 g
DIVIDED BY	
Potency of Methotrexate in decimal (Step 2Ai)	_____
EQUALS	
i. Quantity of Methotrexate needed for 10 mL Injection	_____ **g**
MULTIPLED BY	
Processing error adjustments (15 to 20%):	1.15 to 1.20
EQUALS	
ii. Quantity of Methotrexate needed *plus* processing error adjustments:	_____ **g**

4. **Powder preparation:**

A. In the given order, sequentially add the following ingredients to the Sterile Water for Injection (8.0 mL *plus* processing error adjustments):

-Benzyl Alcohol
-Methotrexate (amount determined in Step 3Aii)
-Sodium Chloride

Specifications: Continuously mix.

End result: Homogeneous liquid-like dispersion.

Note: Add the next ingredient, once the previous one has been completely added and dispersed.

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5. **pH testing:**

A. Draw an appropriate amount of the mixture (Step 4A).

B. Test the pH of the sample. It should lie between 8.3 and 8.6.

C. If the pH < 8.3, carefully add, in a dropwise fashion, the Sodium Hydroxide 10% Solution to the mixture:

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 8.3 to 8.6 is obtained.

IMPORTANT: Do not allow the pH to rise above 8.6.

D. If the pH > 8.6, carefully add, in a dropwise fashion, the Hydrochloric Acid 10% Solution to the mixture:

1. Draw and transfer 1 or 2 drops of the Hydrochloric Acid 10% Solution to the mixture.
2. Stir for at least 5 minutes to evenly disperse the Hydrochloric Acid 10% Solution.
3. Re-test the pH.
4. Continue to add the Hydrochloric Acid 10% Solution until the pH of 8.3 to 8.6 is obtained.

IMPORTANT: Do not allow the pH to fall below 8.3.

End result: Homogeneous liquid-like **solution**.

6. **Filling to volume:**

A. Add additional Sterile Water For Injection to the above mixture to fill to the required batch size (10.0 mL *plus* processing error adjustments).

Specifications: Continuously mix.

End result: Homogeneous liquid-like solution.

7. **Filtering and transferring:**

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.

8. **Filter integrity test:**

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.

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9.	**Sterility testing:** Validate the Test sample for sterility and endotoxins, in accordance to current USP 797 regulatory guidelines.

SUGGESTED PRESENTATION

Estimated Beyond-Use Date		14 days, refrigerated as per USP 797. BUD based on a successful sterility and endotoxin test result.	Packaging Requirements	Sterile, tightly closed, light-resistant injection vials.
Auxiliary Labels	1	Use as directed. Do not exceed prescribed dose.	7	Discard in the presence of particulate matter.
	2	Keep out of reach of children.	8	Do not use if product changes color.
	3	Keep in a dry place.	9	Consult your health care practitioner if any prescription or over-the-counter medications are currently being used or are prescribed for future use.
	4	Protect from light.	10	Discard container after use.
	5	Keep refrigerated. Do not freeze.	11	May impair mental and/or physical ability. Use care when operating a car or machinery.
	6	Do not take with alcohol, sleep aids, tranquilizers or other CNS depressants.	12	Equilibrate to room temperature before use.
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

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