

Multiple Micronutrient Supplements (MMS) for Pregnant Women

Considerations for Accessing MMS Product Supplies for National Programs

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Topics

- Which MMS product is recommended and why
- Why it is important to concentrate on availability of MMS *immediately*
- Practical information to inform planning for UNIMMAP – MMS product supplies
- Available technical resources



Introduction

Introduction



Multiple Micronutrient
Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

Multiple Micronutrient
Supplementation Task
Force

(MMS – Task Force)

Multiple Micronutrient
Supplementation
Technical Advisory Group

(MMS – TAG)

- Expert body organized within the New York Academy of Sciences (NYAS) and sponsored by the Bill & Melinda Gates Foundation
 - Created to examine specific concerns raised by WHO pertaining to effectiveness, safety, and cost-effectiveness of MMS
- Successor body to the MMS – Task Force
 - Curates and disseminates information to support MMS initiatives that: raise awareness, advocate for its use, formulate policy, and guide implementation

Work product of both groups aims to support and inform decision-making by stakeholders on all aspects of MMS programming – including MMS product related issues

Which MMS Product is Recommended for Use in Public Health Nutrition Programs and Why

Which MMS Product and Why

The MMS – Task Force recommends the UNIMMAP formulation of MMS for national programs:

- **UNIMMAP** is the **United Nations International Multiple Micronutrient Antenatal Preparation**
- Developed by WHO/UNICEF/UNU during a workshop in 1999 convened to identify a formula for use in efficacy trials¹
- 1995 – 2013: 21 clinical trials were undertaken to compare efficacy of MMS to iron and folic acid supplements (IFAS)
- Evidence shows MMS has positive effects on maternal health and pregnancy outcomes² as compared to IFAS, is **safe**, is **cost-effective**, and **affordable**

Which MMS Product and Why

The MMS – TAG deliberations:

- Use MMS **without variation from the UNIMMAP formula:**
 - UNIMMAP – MMS is proven effective in clinical trials
 - Difficult to define what constitutes a “similar” product
- **UNIMMAP – MMS formula be fixed for foreseeable future:**
 - Provides certainty to manufacturers and health services
 - Health services should wait to add ingredients until benefits of additional ingredients and/or a re-formulation are clinically demonstrated
- Provision of **180 doses of MMS during pregnancy;** starting MMS use as early in pregnancy as possible

Which MMS Product and Why

The UNIMMAP Formula:

Ingredient	UNIMMAP Specification
Vitamin A	800 mcg RE
Vitamin C	70 mg
Vitamin D	5 mcg (200 IU)
Vitamin E	10 mcg α -TE (tocopherol equivalents)
Vitamin B1 (Thiamine)	1.4 mg
Vitamin B2 (Riboflavin)	1.4 mg
Vitamin B3 (Niacinamide)	18 mg
Vitamin B6 (Pyridoxine)	1.9 mg
Folic Acid	400 mcg
Vitamin B12	2.6 mcg
Iron	30 mg
Iodine	150 mcg
Zinc	15 mg
Selenium	65 mcg
Copper	2 mg

**Why is it Important to
Concentrate on Availability of
MMS Product Supply
*Immediately***

Why Focus Immediately on the MMS Product Supply

Global Demand for MMS is meaningful and growing:

- **Potential need** for MMS in LMICs alone is **≈197 m pregnancies/year**
- **Available MMS product supplies currently support ≈4 m pregnant women/year use MMS in LMICs** (ex-UNICEF data)
- **User demand expected to at least double** in near future as a result of initiatives generating momentum:
 - **≈64 countries** (including **≈20 governments**) exploring MMS use
 - **Advocacy initiatives**
 - **High visibility demonstration projects**
 - **Growing technical assistance capacity** being deployed to advance planning
- **Bottom line:** Future potential demand is large; current demand already equals or exceeds available global supply

Why Focus Immediately on the MMS Product Supply

Accessing UNIMMAP – MMS:

- ❖ Rate-limiting step when operationalizing policy
- ❖ Stakeholders uniformly underestimate time to activate new manufacturing  **1- 3 years**
- Few manufacturers produce the UNIMMAP – MMS anywhere
- UNIMMAP – MMS (as any new formulation) is considered in industry as a **“custom” product**; and requires considerable lead time to define, test manufacture, and produce at volume
- MMS being introduced into public health nutrition programs is anticipated to be on a very large scale – implying:
 - Substantial new manufacturing capacity is required, and
 - Each new manufacturer will produce MMS as a “custom” product

Practical Information to Inform Planning to Access UNIMMAP – MMS Supplies

Existing Sources

Benchmark Price for UNIMMAP – MMS

When is domestic manufacturing justified

What should constitute a qualified manufacturer

Open-access UNIMMAP – MMS Product Specification

Practical Information for Planning Access to UNIMMAP – MMS

Existing sources of donated UNIMMAP – MMS manufactured to international quality standards:

- **Finished product donations:**
 - Kirk Humanitarian (USA)
 - The Vitamin Angel Alliance (USA)
 - UNICEF
- **Subsidized purchases of finished product:**
 - Kirk Humanitarian (USA)

Practical Information for Planning Access to UNIMMAP – MMS

Existing sources selling UNIMMAP – MMS manufactured to international quality standards:

- **Commercial sales of finished product:**
 - Contract Pharmacal Corporation (USA)
 - Lomapharm (Germany)
 - Lekepharm (Denmark)
 - Beximco (Bangladesh – currently manufactures only for clinical trails)
- **Commercial sales of Pre-mix:** a pre-mix of ingredients is potentially very useful for new manufacturers, and is available to finished product manufacturers (DSM)

Practical Information for Planning Access to UNIMMAP – MMS

Benchmark Pricing for UNIMMAP – MMS:

- Cost-effectiveness of UNIMMAP – MMS is demonstrated
- MMS has been priced **5-15x IFA manufactured to a similar international quality**
- Even with higher pricing, MMS is still among the most **cost-effective antenatal care interventions**; but **price is still important**
- Dramatic price reductions have been achieved over the past 5 years:
 - UNIMMAP – **MMS is at cost-parity** with IFA supplements of similar quality
 - Benchmark pricing for UNIMMAP – MMS of **U.S. \$0.01** per tablet is reached at a **volume/year of 3-5 million, 180 count bottles**

UNIMMAP MULTIPLE MICRONUTRIENT SUPPLEMENTS (MMS) FOR PREGNANT WOMEN

PACKAGING OPTIONS, COST AND ENVIRONMENTAL IMPACT

	 180 Count	 30 Count	 30 Count	 Bulk¹
PACKAGING FEATURES	Child-resistant and tamper-proof HDPE bottle	Child-resistant and tamper-proof HDPE bottle	Child-resistant and tamper-proof aclar film with foil	Variable
PRODUCT COST Per tablet ^{2,3}	1.1 cents Palletization costs an added .05 cents per bottle.	2 cents Palletization costs an added .01 cent per bottle.	1.7 cents Palletization costs an added .01 cent per card.	0.9 cents Repackaging costs are variable.
ENVIRONMENTAL IMPLICATIONS Per million women (180 doses each) ⁴	Total waste: 50,486 lbs	Total waste: 216,935 lbs	Total waste⁵: 85,663 lbs	Total waste: 29,537 lbs
AVAILABILITY	Available now. Approved in the U.S. and commercially available now.	Not currently available. Each variation to the core UNIMMAP MMS product (180-count bottle) is considered a “custom” product that will require new stability studies and significant manufacturing preparation to make that will vary by country regulatory requirements. Variations from currently available units are estimated to take at least 18-24 months until obtainable for commercial use.		



¹ MMS shipped in bulk requires repackaging before dissemination (business-to-business (B2B) option).

² Prices are based on a high-volume guarantee. The product cost is higher for customers who buy the MOQ (minimum order quantity) of 100,000 bottles.

³ The current MMS Taskforce recommendation for MMS dosing is 180 tablets per pregnancy beginning as early as possible.

⁴ Data provided by Contract Pharmacal Corporation (CPC), 2019.

⁵ It is more difficult and more costly to recycle aclar film and foil than it is to recycle HDPE bottles.

UNIMMAP multiple micronutrient supplements (MMS) contain 15 vitamins and minerals consistent with antenatal micronutrient standards that women need to help ensure a healthy pregnancy and a healthy baby.

Practical Information for Planning Access to UNIMMAP – MMS

Benchmark Pricing for UNIMMAP – MMS:

- The **benchmark price** achieved by global suppliers will be **difficult to replicate** by those manufacturing for a single domestic market:
 - **Few countries have annual product demand** needed to achieve economies of scale in manufacturing (e.g., \approx 3-5 million pregnancies)
 - Most **manufacturers don't have volume capacity** needed to produce at economies of scale
 - **Ingredients are generally not locally available**; and associated **import fees & excise taxes have a significant** effect on final price
- Nevertheless, negotiations with manufacturers operating in a single domestic market should be entered into recognizing benchmark pricing for a fixed high quality UNIMMAP – MMS product

Practical Information for Planning Access to UNIMMAP – MMS

When is domestic manufacturing justified:

- Many factors contribute to a decision to undertake or require domestic manufacturing
- Domestic stakeholders must determine for themselves when its appropriate to require sourcing from a domestic manufacturer
- Intuitive basic requirements:
 - There are **qualified** domestic manufacturers with **moderate to high volume capacity** to produce UNIMMAP – MMS
 - When the number of pregnancies reaches 3-5 million per year

NB. This argument is enhanced when domestic manufacturing capacity can be harnessed to supply an export market

Practical Information for Planning Access to UNIMMAP – MMS

What constitutes a “qualified manufacturer”. The MMS – TAG recommends that manufacturers:

- Possess current tablet and/or capsule manufacturing experience and know-how
- Regularly manufacture to internationally recognized quality standards
- Can manufacture consistent with the **open-access UNIMMAP – MMS product specification**

Practical Information for Planning Access to UNIMMAP – MMS

A Product Specification – What is it, how is it used, why is it important:

- UNIMMAP – MMS product formula is publicly available, but is insufficient to support manufacturing
- A product specification defines the exact product:
 - Ingredients, product formula, and finished product characteristics
 - Label claims & regulatory requirements to be met and the certifications/documentation required to support label claims
 - Reference standards and methods to be used to verify product conformance with standards
- **The product specification** is appended to a purchase agreement; ensures both parties understand what product is being produced and how the finished product will be authenticated

Practical Information for Planning Access to UNIMMAP – MMS

Comparing “proprietary” vs “open-access” product specifications:

- Most product specifications are proprietary, and not readily available to other manufacturers or purchasers
- Open-access product specification is available to all & designed to speed product development, reduce product cost, and mitigate product related concerns that buyers might have if product comes from different donors/manufacturers

A consensus open-access product specification for UNIMMAP – MMS is developed, and will be released at the Micronutrient Forum’s 5th Global Conference (Bangkok March 23rd) and published in the Annals of the New York Academy of Sciences

Practical Information for Planning Access to UNIMMAP – MMS

Synchronizing product supplies needed for immediate use and to fulfill long-term needs:

- Introduction phase of national programs (Months 1 - 12)
 - Product donated from Kirk Humanitarian, Vitamin Angels, or UNICEF is main avenue for access, but supplies are limited
 - Product purchased directly from a qualified manufacturer and imported is a second option; existing commercial manufacturers have an ability to scale existing production
- Scaling phase of national programs (Months 12 - 24)
 - Procurement of MMS is the main option for national programs and should be given a 1 to 2-year lead time to secure if imported
 - Procurement from local manufacturer may be appropriate for selected countries, but requires a 1 to 3-year lead time

Available Resources

Available Resources



CONSENSUS OPEN-ACCESS UNIMMAP-MMS PRODUCT SPECIFICATION



1 Product Description ¹

The product defined by the following specification conforms to The United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) formula and is a Multiple Micronutrient Supplement (MMS) for pregnant women that is delivered in the form of a film coated tablet.²

2 Ingredients

2.1 Food/Dietary/Nutritional Ingredients ³

Table 1 shows the food/dietary/nutritional ingredients used in the UNIMMAP formulation and should be prepared from ingredients that meet *United States Pharmacopeia (USP)* or other globally recognized pharmacopeia compendial standards. Where such standards do not exist, ingredients may be used in the UNIMMAP formulation if they have been shown to be of acceptable food grade quality using other suitable procedures.

Table 1. Recommended Food/Dietary/Nutritional Ingredients

Component	Chemical Entity [*]	Amount
Vitamin A	Retinyl Acetate	800 mcg RAE
Vitamin C	Ascorbic Acid	70 mg
Vitamin D	Cholecalciferol	5 mcg (200 IU)
Vitamin E	Alpha Tocopheryl Succinate	10 mg α-TE
Vitamin B1	Thiamine Mononitrate	1.4 mg
Vitamin B2	Riboflavin	1.4 mg
Vitamin B3	Niacinamide	18 mg NE
Vitamin B6	Pyridoxine HCl	1.9 mg
Folic Acid	Folic Acid	680 mcg DFE (400 mcg)
Vitamin B12	Cyanocobalamin	2.6 mcg
Iron	Ferrous Fumarate	30 mg
Iodine	Potassium Iodide	150 mcg
Zinc	Zinc Oxide	15 mg
Selenium	Sodium Selenite	65 mcg
Copper	Cupric Oxide	2 mg

* These chemical entities may be replaced by other chemical entities if they demonstrate equal or better performance (e.g., stability).

2.2 Excipients

Excipients used in the UNIMMAP formulation generally are prepared from ingredients that meet *USP, NF, Food Chemical Codex*, or other globally recognized pharmacopeia compendial

MMS – TAG Resources

The MMS – TAG has a range of resources available to support efforts to introduce MMS:

- **General:** <https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources>
- **Evidence – Key Scientific Papers:**
 - [2016 WHO Guidelines for Antenatal Care](#)
 - [2017 Cochrane Review](#)
 - [2017 Lancet GH Review](#)
 - [New Evidence Should Inform WHO Guidelines on MMS in Pregnancy](#)
 - [Review of the evidence regarding the use of MMS in low- and middle-income countries](#)
 - [Replacing IFA with MMS among pregnant women in Bangladesh and Burkina Faso: costs, impacts, and cost-effectiveness](#)
 - [The upper level: examining the risk of excess micronutrient intake in pregnancy from antenatal supplements](#)
 - [Benefits of MMS supplementation in pregnancy](#)

MMS – TAG Resources

The MMS – TAG has a range of resources available to support efforts to introduce MMS:

- **Technical Resource Materials:**
 - [TRM I: Technical Brief for Policy Makers](#)
 - [TRM II: Training Materials](#)
 - [TRM III: Logistics of Implementation](#)
 - [FAQ](#)
- **Manufacturing Resources:**
 - Open-Access UNIMMAP – MMS Product Specification
- **Implementation Research priorities:**
 - Child Health & Research Initiative methodology [CHNRI exercise](#)
 - Publication of the PROSPERO [protocol for the ongoing systematic review](#) on interventions to increase adherence to micronutrient supplementation during pregnancy

Thank You

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References

References:

¹ Composition of a multi-micronutrient supplement to be used in pilot programs among pregnant women in developing countries. A report of a United Nations Children's Fund (UNICEF), World Health Organization (WHO), United Nations University (UNU) Workshop held at UNICEF Headquarters, New York, July 9, 1999

² Review of the Evidence Regarding the Use of Antenatal Multiple Micronutrient Supplementation in Low- and Middle-Income Countries. Annals of the New York Academy of Sciences, 2019

References

Composition of a Multi-Micronutrient Supplement to be used in Pilot Programmes among Pregnant Women in Developing Countries

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