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 Task Force
(MMS – Task Force)

- 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

Multiple Micronutrient Supplementation Technical Advisory Group
(MMS – TAG)

- 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 trials\(^1\)

• 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 outcomes\(^2\) as compared to IFAS, is **safe**, is **cost-effective**, and **affordable**
Which MMS Product and Why

The MMS – TAG deliberations:

• Use MMS \textbf{without variation from the UNIMMAP formula}:  
  - UNIMMAP – MMS is proven effective in clinical trials  
  - Difficult to define what constitutes a “similar” product

• \textbf{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 \textbf{180 doses of MMS during pregnancy}; starting MMS use as early in pregnancy as possible
## Which MMS Product and Why

**The UNIMMAP Formula:**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>UNIMMAP Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>800 mcg RE</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>70 mg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>5 mcg (200 IU)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>10 mcg α-TE (tocopherol equivalents)</td>
</tr>
<tr>
<td>Vitamin B1 (Thiamine)</td>
<td>1.4 mg</td>
</tr>
<tr>
<td>Vitamin B2 (Riboflavin)</td>
<td>1.4 mg</td>
</tr>
<tr>
<td>Vitamin B3 (Niacinamide)</td>
<td>18 mg</td>
</tr>
<tr>
<td>Vitamin B6 (Pyridoxine)</td>
<td>1.9 mg</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>400 mcg</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>2.6 mcg</td>
</tr>
<tr>
<td>Iron</td>
<td>30 mg</td>
</tr>
<tr>
<td>Iodine</td>
<td>150 mcg</td>
</tr>
<tr>
<td>Zinc</td>
<td>15 mg</td>
</tr>
<tr>
<td>Selenium</td>
<td>65 mcg</td>
</tr>
<tr>
<td>Copper</td>
<td>2 mg</td>
</tr>
</tbody>
</table>
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 $\approx 197$ m pregnancies/year
- Available MMS product supplies currently support $\approx 4$ 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:
  - $\approx 64$ countries (including $\approx 20$ 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 \textit{“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 \textit{“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 trials)

• **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

<table>
<thead>
<tr>
<th>Packaging</th>
<th>Features</th>
<th>Cost</th>
<th>Environmental Impact</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 Count</td>
<td>Child-resistant and tamper-proof HDPE bottle</td>
<td>1.1 cents</td>
<td>Total waste: 50,486 lbs</td>
<td>Available now. Approved in the U.S. and commercially available now.</td>
</tr>
<tr>
<td>30 Count</td>
<td>Child-resistant and tamper-proof HDPE bottle</td>
<td>2 cents</td>
<td>Total waste: 216,935 lbs</td>
<td></td>
</tr>
<tr>
<td>30 Count</td>
<td>Child-resistant and tamper-proof aclar film with foil</td>
<td>1.7 cents</td>
<td>Total waste: 85,663 lbs</td>
<td></td>
</tr>
<tr>
<td>Bulk</td>
<td>Variable</td>
<td>0.9 cents</td>
<td>Total waste: 29,537 lbs</td>
<td>Not currently available. Each variation to the core UNIMMAP MMS product (180-count bottle) is considered a &quot;custom&quot; 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.</td>
</tr>
</tbody>
</table>

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.
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.
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., ≈ 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
When is domestic manufacturing justified:

- Many factors contribute to a decision to undertake or require domestic manufacturing
- Domestic stakeholders must determine for themselves when it's 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
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
1 Product Description

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 Ingredients

2.1 Food/Dietary/Nutritional Ingredients

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

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

* 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 standards.
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
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

Clayton A. Ajello, DRPH, MPH
Senior Technical Advisor, Vitamin Angels
References

References:


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


Held at UNICEF Headquarters, New York July 9, 1999

References