Expert Consensus on an Open-Access Product Specification for MMS for Pregnant Women

A globally adaptable specification supplied to public health nutrition programs

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Key messages

- A complete product specification can serve as the basis of a quality agreement between a purchaser and a manufacturer. It provides a common and transparent technical understanding of the requirements for a product (and its packaging) to be manufactured and the means and methods by which both parties can verify that the product delivered for distribution is in fact the product that was ordered.

- The product specification is generally a proprietary document owned by either the purchaser or the manufacturer, and is often difficult for third parties to access. By contrast, an open-access product specification is freely available to any interested party and delivers benefits to both the purchaser and the manufacturer that help facilitate the initiation and scaling of important public health programs.

- A consensus open-access product specification for the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) formulation of a multiple micronutrient supplement (MMS) for pregnant women has been developed and is made available in summary form in this contribution. The full version is available for download from Sight and Life (sightandlife.org/wp-content/uploads/2020/04/SightandLife_SpecialReport_ExpertMMS_.pdf) and the New York Academy of Sciences MMS Technical Advisory Group (MMS TAG), www.nyas.org/media/21537/expert-consensus-on-an-open-access-unimmap-mms-prod-spec.pdf, the Micronutrient Forum and Vitamin Angels; it provides an important contribution towards accelerating the availability of UNIMMAP-MMS for global public health nutrition programs.

- The open-access product specification for the UNIMMAP-MMS product is intended to be used globally by purchasers of UNIMMAP-MMS and by qualified manufacturers; it attempts to anticipate and address all of the MMS product/packaging specifications that most governments would include for a nutritional supplement to be placed on an essential medicines list, if and when they seek to transition from distributing iron and folic acid (IFA) supplements to MMS for pregnant women.

- Several insights that will be useful to both purchasers and manufacturers are offered at the conclusion of this article; these are the result of the decade-long journey it has taken to achieve a consensus on the UNIMMAP-MMS open-access product specification.

Introduction

Multiple micronutrient supplements (MMS) for pregnant women provide women and their babies with a positive pregnancy experience and healthy start to life beyond that which can be achieved with IFA supplements alone.1,2,3 Clinical trials to date have compared IFA with MMS, most often using the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) MMS formula. UNIMMAP-MMS was developed by experts during a workshop organized by WHO, UNICEF and the United Nations University in 1999, and convened to identify an MMS formula for efficacy/clinical trials.4 Recently, UNIMMAP-MMS was recommended by the Task Force for MMS for Pregnant Women as the standard MMS formulation to be used in public health nutrition programs for pregnant women.3
“Recently, UNIMMAP-MMS was recommended as the standard MMS formulation to be used in public health nutrition programs for pregnant women”

With UNIMMAP-MMS proven to be efficacious, safe, cost-effective and affordable for public health nutrition programs, as reported elsewhere in this *Sight and Life* Special Report, the challenge turns to implementation and scaling the manufacture and distribution of MMS on a global scale. The nearly 200 million pregnancies occurring annually in low- and middle-income countries (LMICs) are most likely to benefit from the use of UNIMMAP-MMS. If most or all pregnant women in LMICs were to begin MMS use in early pregnancy and follow the recommended regimen of one tablet per day, equivalent to 180 tablets per pregnancy, there would be a total annual demand for more than 35 billion tablets for pregnant women in LMICs alone. ³ Producing 35 billion tablets per year is a significant manufacturing challenge that would require several manufacturers to fulfill it. Apart from the large volume required, an equally daunting task is to ensure consistency in the quality of an affordable MMS across various public health nutrition programs while allowing for variances in global manufacturing attributable to variations among internationally recognized regulatory and pharmacopoeia standards.

While the UNIMMAP-MMS formula is publicly available, alone, it is insufficient to characterize the quality aspects of an MMS product in a way that is useful for both manufacturers and purchasers. A product specification is customarily used by both purchasers and manufacturers to achieve a common understanding of the product that is to be manufactured and purchased.

**What is a product specification?**

A product specification is a technical document that provides a detailed description of the product to be manufactured. For UNIMMAP-MMS, it defines the specifications pertaining to the MMS product’s formula (i.e., UNIMMAP formula) including: the amount and chemical form of each ingredient; the dosage form (e.g., tablet, capsule); the packaging container-closure system (e.g., bottle, blister pack); the tests, testing methods and reference standards, and acceptance criteria to be applied to the finished product to verify quantitative label claims; stability study requirements; and any third-party certifications expected of the manufacturer.

The primary function of a product specification is to support a procurement transaction. It serves as the basis for a ‘quality agreement’ between the purchaser and the manufacturer, providing both parties with a common and transparent technical understanding of the requirements for a product to be manufactured and the means and methods by which both parties can verify that the product delivered for distribution is in fact the product that was ordered.

“**The primary function of a product specification is to support a procurement transaction**”

**Why is an open-access product specification needed?**

A product specification is generally a proprietary document, owned by either the purchaser or the manufacturer, or else it might be accessed under a licensing arrangement with a third-party owner. An open-access product specification is freely available to any interested party, and is important for products used in public health programs requiring a product to be of high quality, available in high volume and procurable at a low cost. An open-access product specification – especially one that can be adapted for use everywhere – can play an important role in accelerating and maintaining the availability of UNIMMAP-MMS for global public health programs where multiple manufacturers are expected to play a role in meeting demand for product supply. The key benefits of an open-access product specification are described in **Box 1**.

**BOX 1: Benefits of an open-access product specification for UNIMMAP-MMS**

**Purchaser-derived benefits:**

- Gives users of donated or purchased product confidence that the product accessed is the clinically proven UNIMMAP-MMS product when introducing MMS into public health nutrition programs.
- Provides assurance – when verified by an independent verification process arranged by the purchaser for this purpose – that a product is made to the specification that conforms to international quality standards expected by large and responsible healthcare systems.
- Fosters confidence through the knowledge that it is the same product used most often in clinical trials and proven effective.
- Helps purchasers to focus negotiations with manufacturers on volume and price for a product of fixed or defined quality.

**Manufacturer-derived benefits:**

- Reduces time and investment needed to deliver a finished product to one or more purchasers by avoiding the need to recreate a product description.
• Provides direction pertaining to allowable variances in a product of defined quality that are attributable to different regulatory and pharmacopoeia requirements in different regions of the world.
• Defines other variances that might be sought by a purchaser and helps manufacturers assist purchasers to understand the impact of those variances on both cost and environmental impact.
• Helps attract interest from different potential purchasers that can result in multiple simultaneous orders, which in turn can lower manufacturing costs.

Who should use the open-access product specification?
The open-access product specification is intended for UNIMMAP-MMS purchasers, procurement agents (e.g., donor agencies, foundations, NGOs, governments, bilateral agencies and multilateral agencies) and manufacturers accessing or producing the MMS product for large-scale public health nutrition programs. It is intended as a resource for parties to the procurement process to: (1) inform discussions and help place purchasers and manufacturers on an equal footing; (2) foster transactions that result in procurement of a product of fixed, high quality at a price fair to both purchaser and manufacturer; and (3) enable production of a UNIMMAP–MMS product to globally recognized quality standards by many manufacturers.

“Purchasers and manufacturers should work collaboratively using the product specification”

How should the open-access product specification be used?
Both purchasers and manufacturers should use the specification as the basis for a quality agreement and include it as an attachment to a purchase agreement. It is designed to be adaptable to conform to any globally recognized regulatory regime and pharmacopoeia as defined in the specification. Purchasers and manufacturers should work collaboratively using the product specification to agree on technical requirements acceptable to the purchaser with an understanding, provided by the manufacturer, of the cost implications of each decision. The specification can also be used to assess the capabilities of prospective manufacturers. The key criteria that should be met by manufacturers presenting themselves as qualified to bid on procurement contracts for UNIMMAP-MMS are shown in Box 2.

The open-access UNIMMAP-MMS product specification also serves as a reference standard underlying benchmark pricing. Currently, UNIMMAP-MMS can be produced in the USA to the UNIMMAP–MMS product to globally recognized quality standards. It is intended as a resource for parties to the procurement process to:

- Help avert the need to redact the product specification for different potential purchasers
- Foster transactions that result in procurement of a product of fixed, high quality at a price fair to both purchaser and manufacturer
- Enable production of a UNIMMAP–MMS product to globally recognized quality standards by many manufacturers

Manufacturers who:
- Possess current tablet and/or capsule manufacturing experience, expertise, and knowledge.
- Manufacture products according to current Good Manufacturing Practice (cGMP) regulations promulgated by an internationally recognized regulatory authority (e.g., US FDA), or by other Stringent Regulatory Authorities (e.g., WHO), by a PIC/S member, or by a globally recognized authority (e.g., USP), including but not limited to:
  > US FDA 21 CFR Part 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements;
- Have a verifiable capacity to manufacture to the consensus open-access UNIMMAP–MMS product specification (see Box 3).

MAP-MMS open-access product specification for about US$0.01 per tablet (with orders of 3–5 million, 180-count bottles) using the regulatory framework of the US Food and Drug Administration (US FDA) and the quality standards of the United States Pharmacopeia (USP). This pricing can serve as a benchmark for manufacturing in other parts of the world; however, it must be recognized that prices available from global manufacturers and those from manufacturers producing for a single domestic market will vary, depending upon a number of factors (e.g., volume capacity of the manufacturer, volume of product purchased, packaging option selected, local taxes, and the regulatory and pharmacopoeia framework selected).

The consensus open-access UNIMMAP–MMS product specification
An expert consensus on an open-access UNIMMAP-MMS product specification was recently achieved through a Technical Consultation jointly hosted by the New York Academy of Sciences Multiple Micronutrient Supplementation Technical Advisory Group (MMS TAG) and the Micronutrient Forum, with funding from the Bill & Melinda Gates Foundation. The key components of the specification are summarized in Box 3. The full version of the consensus open-access UNIMMAP-MMS product specification is available for download from Sight and Life, the New York Academy of Sciences MMS TAG, the Micronutrient Forum and Vitamin Angels.

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**Box 3: Key technical components of the consensus open-access product specification for a UNIMMAP-MMS product**

The complete specification is available for download from Sight and Life, the New York Academy of Science MMS Technical Advisory Group (MMS TAG), the Micronutrient Forum and Vitamin Angels: www.nyas.org/media/21537/expert-consensus-on-an-open-access-unimmap-mms-prod-spec.pdf.

1. **General product description and formula:** tablets conforming to UNIMMAP formula.
2. **Ingredients:** including food/dietary/nutritional ingredients, excipients and processing aids.
3. **Stability studies:** required to support key label claims (stated or implied).
4. **Packaging/labeling:** 180-count HDPE (high-density polyethylene), tamper-evident, child-resistant bottle (possible alternatives for specialized circumstances, although not recommended here for regular use, are: 30-count HDPE bottle and 30-count blister pack).
5. **Manufacturing standards and certificates:**
   5.1. **Pharmacopoeia standards:** globally recognized.
   5.2. **Certificate of Analysis (CoA):** verifies conformance to product specification.
   5.3. **Certificate of Origin:** verification of manufacturer’s country of origin.
   5.4. **Certificate of Free Sale (CFS) (as required):** verification that product can be used in the country of manufacture.
   5.5. **Certificate of current Good Manufacturing Practices (cGMP):** verification product is manufactured in accordance with standards promulgated by an internationally recognized regulatory/scientific authority.
   5.6. **Halal Certification (as needed):** verifies conformance with IFANCA standards or a similar Islamic certifying body.
6. **Other documentation required:** includes documentation pertaining to change control notification.
7. **Finished product specifications for product identification, performance and purity:**
   7.1. Tablet characterization and purity, including tests, test methods and acceptance criteria.
   7.2. Potency assay requirements (per tablet), including form of each ingredient, test method, label claim and limit references.
8. **Analytical test methods:** validated or verified, as needed.
9. **Storage and transportation requirements.**
10. **Definitions.**

**“The journey to reach the consensus open-access product specification started nearly a decade ago”**

The journey to reach the consensus open-access product specification started nearly a decade ago. With emerging evidence on the benefits of MMS, Kirk Humanitarian and Vitamin Angels – each having worked separately at first – began a collaboration in 2016 to develop an MMS product that would be both of high quality and acceptable to grantees (including both governments and NGOs) already seeking a supply of MMS to explore its use.⁶,⁷ Working with multiple manufacturers within and outside the USA, several independent consultants and the USP, an initial UNIMMAP-MMS product specification was developed. A key factor prompting its development was recognition that: (1) demand for MMS existed, but the supply was negligible; (2) the existing product cost seemed high and susceptible to significant reduction through contract manufacturing; and (3) the existing product specifications were proprietary and inaccessible. During a presentation of the specification (to present and explain its use and value) to about 35 people from a range of organizations (including manufacturers, purchasers, program implementers and funders) held in conjunction with the Women Deliver Conference in Vancouver, Canada (5 June 2019), participants recognized it as a credible interim open-access product specification, and recommended it be subjected to review by experts through an independent technical consultation. That expert review – the MMS Product Specification Technical Consultation – was subsequently co-hosted by the New York Academy of Sciences and the Micronutrient Forum on 11–12 November 2019 in Washington, DC.

**Securing a UNIMMAP-MMS product supply for immediate and long-term needs: global manufacturers versus manufacturing for a single domestic market using the open-access UNIMMAP-MMS product specification**

When large healthcare systems in a single domestic market contemplate the purchase of a locally manufactured UNIMMAP-MMS product (as compared with importation from a global manufacturer), a local manufacturer’s product can conform with the open-access specification by applying any of the internationally recognized manufacturing standards generally used in their region of the world. Where large healthcare systems seek to activate a program quickly when domestic manufacturing is not yet available, there is a pathway for gaining immediate access to UNIMMAP-MMS (based on the open-access product specification) while building capacity for manufacturing in a single domestic market using the same open-access product specifications (see Box 4).
**BOX 4: Proposed pathway to local manufacturing of UNIMMAP-MMS synchronized with MMS introduction**

- **Step 1:** Initial dependence by a health system purchaser on donated finished MMS product (packaged for individual use) from reputable international donation programs during the introductory stages when local authorities are engaged in a large-scale implementation to understand how to effectively and efficiently introduce and scale UNIMMAP-MMS. For example, using a demonstration program to explore ways to strengthen existing antenatal care services, or by exploring ways to increase adherence to the MMS regimen of 180 tablets per pregnancy as compared with adherence achieved using IFA supplementation alone. Additionally, during this step, long-term procurement options and/or domestic manufacturing are explored.

- **Step 2:** Importation and redistribution by a local manufacturer (i.e., a de facto distributor in this case) of finished product packaged for individual use (for use in initial introduction activities), while stability studies are undertaken simultaneously to permit the importation of finished product in bulk that can be repackaged and redistributed for individual use by a local manufacturer (also for use in initial introduction activities). Involving qualified local manufacturers in the opportunity to be the importer and repackager of an imported product can be an important incentive and step for manufacturer(s) that seek to become a local manufacturer. This two-step process provides a useful role for local manufacturers while they are building out their capacity to manufacture the product locally to the defined open-access UNIMMAP-MMS product specification, working to add the product to the national essential medicines list and securing local registration of the product.

- **Step 3:** Local purchase of UNIMMAP-MMS when a local manufacturer (producing for a single domestic market) demonstrates the ability to manufacture to the open-access product specification – a goal that might be facilitated by using a premix of UNIMMAP ingredients. Where manufacturing for a single domestic market is desired, local officials should recognize that building capacity to deliver a product to the open-access product specification takes time – time that is uniformly underestimated by decision-makers. Depending upon the starting point of the manufacturer, it can often take 12–36 months or more to reach local manufacturing potential.

**Note:** in all cases, purchasers (or grantees receiving UNIMMAP-MMS) should seek to use product that meets the product specifications in the open-access product specification, recognizing that the specification provides regional options for regulatory and pharmacopoeia standards applied.

While the decision to manufacture in a single domestic market is affected by a range of factors, local manufacturing can remain highly cost-effective if the product is manufactured in moderate to high volume (e.g., the optimal volume for gaining economies of scale is achieved when producing product for at least 3–5 million pregnancies annually).

**“With consensus around the UNIMMAP–MMS open-access product specification now achieved, purchasers and manufacturers everywhere can benefit from its immediate use”**

**Insights derived during the development of a consensus open-access UNIMMAP-MMS product specification**

With consensus around the UNIMMAP-MMS open-access product specification now achieved, purchasers and manufacturers everywhere can benefit from its immediate use. Apart from its use as described in this paper, large healthcare systems and manufacturers can benefit from the aggregated insights derived during the journey to achieve a consensus product specification – as summarized in **Box 5**.

**BOX 5: Key insights derived during the journey to achieve a consensus open-access UNIMMAP-MMS product specification**

- When large healthcare systems, especially national health services, have decided to begin to explore a transition from IFA for pregnant women to MMS, there should be vigorous discussion and early planning to consider how to gain access to an affordable, high-quality UNIMMAP-MMS product. A local MMS task force can provide an important forum to examine this issue (along with many others), which represents the first – and critical – rate-limiting step to any transition from IFA to MMS, even for the initial exploration and introduction of MMS. No program can effectively and...
efficiently get underway without the UNIMMAP-MMS product or a plan to access the product.

- At the outset of 2020, there are only two or three existing manufacturers of UNIMMAP-MMS globally with the immediate or potential capacity to fulfill orders for UNIMMAP-MMS.
- Many more manufacturers will be required to fulfill the demand for UNIMMAP-MMS. Irrespective of how well qualified a prospective manufacturer is, or where they are based, it generally takes two or more years for a qualified manufacturer to achieve volume production of a product that meets the open-access UNIMMAP-MMS product specification.
- The benchmark price of about US$0.01 per tablet of UNIMMAP-MMS can be achieved when manufacturing capacity reaches 3–5 million, 180-count bottles of UNIMMAP-MMS product production per year. While some cost reduction occurs beyond this volume, an optimal economy of scale appears to be reached, and there is only limited incremental benefit in producing product for beyond 5 million pregnancies per year.
- Many nations may seek to develop or require local manufacturing of UNIMMAP-MMS for domestic needs for a variety of reasons. However, the benchmark price realized by global suppliers will be difficult to replicate by those manufacturing for a single, domestic market, because:
  - few countries actually have a demand for the volume of MMS product needed to achieve economies of scale;
  - most manufacturers do not have the capacity to produce the volume of MMS needed to achieve economies of scale; and
  - most LMIC manufacturers must import MMS ingredients, incurring significant import fees and excise taxes that significantly increase the price of the finished product.
- When any qualified manufacturer is making UNIMMAP-MMS for the first time, it is important for the purchaser to have an independently operated ‘verification’ program in place to verify manufacturing processes and the quality of the final product before the product is used; and it is prudent to keep the verification program in place over time.
- Where national governments seek to make a transition from IFA supplementation to MMS, and eventually use locally manufactured UNIMMAP-MMS product to satisfy local domestic demand, decision-makers can consider various options for accessing MMS product while developing and implementing a local procurement strategy. See Box 4 for a road map of options to local manufacturing. The most important aspect of accessing UNIMMAP-MMS for large-scale programs (irrespective of whether the product is obtained through importation or local manufacturing) is for decision-makers to have a sustainable plan for accessing UNIMMAP-MMS. Such a plan is likely to include donated product during an introductory or transition period, but need not (and cannot) be based, exclusively, on long-term access to donated product. Financially sustainable access to UNIMMAP-MMS should not be problematic for most national health services since they already purchase IFA, and the current pricing of UNIMMAP-MMS is on par with that of IFA manufactured to similar international quality standards.
- Where local manufacturing for a domestic market is sought, it is especially important for local manufacturers to use open-access UNIMMAP-MMS Product specification if a national producer seeks to manufacture for export within their region.
- When planning a transition from IFA to MMS, it is important for local regulatory authorities to be involved with other stakeholders within a local MMS task force; and local regulatory bodies can benefit from reviewing the consensus open-access UNIMMAP-MMS product specification early as efforts are undertaken to include UNIMMAP-MMS in the local essential medicines list.
- Using the consensus open-access UNIMMAP-MMS product specification for a product that is to be used in a public health nutrition program provides significant benefits to purchasers and manufacturers irrespective of their location globally.

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References and notes


The consensus open-access UNIMMAP–MMS product specification referenced here for download is based upon and adapted, with permission, from the open-access MMS product specification originally created by the Vitamin Angel Alliance and revised for global use by a Technical Consultation of experts convened in Washington, DC, on 11–12 November 2019, and hosted jointly by the New York Academy of Sciences Multiple Micronutrient Supplementation Technical Advisory Group (MMS TAG) and the Micronutrient Forum, with funding from the Bill & Melinda Gates Foundation. Technical Consultation participants included:

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- Gisele Atkinson, Council for Responsible Nutrition
- John Atwater, United States Pharmacopeia
- Gilles Bergeron, The New York Academy of Sciences
- Megan Bourassa, The New York Academy of Sciences
- Nita Dalmiya, UNICEF (observer)*
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- Klaus Kraemer, Sight and Life
- Rajiv Kshirsagar, UNICEF (remote observer)*
- Jarno de Lange, Vitamin Angel Alliance
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- Keith West, Johns Hopkins Bloomberg School of Public Health
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* Disclaimer: UNICEF’s role in the Technical Consultation on the consensus open-access UNIMMAP–MMS product specification was solely as an observer and limited to sharing UNICEF’s technical standards/specifications and its process for internal evaluation. Rajiv Kshirsagar participated as a remote observer only for the purpose of delivering a presentation on UNICEF’s technical standards and its internal evaluation process. Nita Dalmiya participated in person as an observer. UNICEF does not endorse, or imply endorsement of the content in this publication, or outcomes of this Technical Consultation.

Kirk Humanitarian is a 501(c)(3) organization whose mission is to accelerate the availability, access, uptake and use of UNIMMAP–MMS among women at risk of undernutrition during pregnancy to create a healthier and more equitable world.

The Vitamin Angel Alliance (DBA Vitamin Angels) is a 501(c)(3) organization that aims to reduce health and economic disparities across the lifespan of individuals living in hard-to-reach populations through effective delivery of evidence-based nutrition interventions. Specifically, Vitamin Angels is a public health nutrition organization that delivers interventions that target the first 1,000 days of life (i.e., from conception to 24 months of age) and children up to five years of age. Vitamin Angels’ model is premised on the reality that national health services are unable to reach all eligible beneficiaries, especially those who reside in marginalized or hard-to-reach communities. Through a range of strategies working with multiple stakeholders, Vitamin Angels coordinates with governments and NGOs to effectively and efficiently fill gaps in coverage.
For a world free from malnutrition.

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