Expert Consensus on an Open-Access UNIMMAP-MMS Product Specification

sightandlife | Special Report

Multiple Micronutrient Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

Micronutrient FORUM

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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, which should be prepared from ingredients that meet *United States Pharmacopeia (USP)* or other globally recognized pharmacopoeia 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.

2.2 Excipients

Excipients used in the UNIMMAP formulation are generally prepared from ingredients that meet USP, National Formulary (NF), Food Chemical Codex, or other globally recognized pharmacopoeia 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.

Ingredients may be added to the UNIMMAP formulation provided that the ingredients comply with applicable regulatory requirements, and do not interfere with the assay and tests prescribed for determining compliance with the bulk or finished UNIMMAP-MMS product specification.

2.3 Processing aids or other materials

Processing aids or other materials used in the manufacture of the UNIMMAP formulation that do not end up in the finished product should have been shown to be of acceptable food-grade quality using suitable procedures.

Potable water must meet, at minimum, all the requirements for drinking water promulgated in the US Environmental Protection Agency's National Primary Drinking Water Regulations (40 CFR Part 141), and any applicable state and local drinking water requirements that are more stringent. For manufacturers outside the USA, potable water that meets equivalent requirements may be acceptable with justification; for example, if it meets the drinking water regulations of the European Union (European Commission Directive 98/93/EC) or the Japan Drinking Water Quality Standards. Water not meeting such requirements should not be permitted for use in the water purification system for *Purified Water*.

3 Stability studies

The UNIMMAP-MMS finished product labeling must state a shelf life (expiration) date that is indicative of the date before which the product is ensured to meet applicable specifications of identity, strength, quality, and purity when stored under labeled conditions. The shelf life (expiration) date must be supported by suitable stability data, following the guidelines in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH Q1A).

A documented ongoing testing program must be designed to monitor the stability characteristics of the UNIMMAP-MMS product, and the results must be used to establish appropriate storage conditions and shelf life (expiration) dates for the UNIMMAP-MMS

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 B_1	Thiamine mononitrate	1.4 mg
Vitamin B_2	Riboflavin	1.4 mg
Vitamin B_3	Niacinamide	18 mg NE
Vitamin B_6	Pyridoxine HCl	1.9 mg
Folic acid	Folic acid	680 mcg DFE (400 mcg)
Vitamin B_{12}	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).

TABLE 2: Recommended ICH testing conditions for all climatic zones

Climatic zone	Climate definition	Mean temperature / Mean partial water vapor pressure*	Derived climatic conditions	Long-term stability	Accelerated stability
I	Temperate	NMT 15°C / LT 11 hPa	21°C / 45% RH	25°C ± 2°C / 60% RH ± 5% RH	40°C ± 2°C / 75% RH ± 5% RH
II	Subtropical, Mediterranean	GT 15°C & NMT 22°C / GT 11 hPa & NMT 18 hPa	25°C / 60% RH	25°C ± 2°C / 60% RH ± 5% RH	40°C ± 2°C / 75% RH ± 5% RH
III	Hot, dry	GT 22°C / LT 15 hPa	30°C / 35% RH	30°C ± 2°C / 35% RH ± 5% RH	40°C ± 2°C / NMT 25%
IVa	Hot, humid	GT 22°C / GT 15 hPa & NMT 27 hPa	30°C / 65% RH	30°C ± 2°C / 65% RH ± 5% RH	40°C ± 2°C / 75% RH ± 5% RH
IVb	Hot and very humid	GT 22°C / GT 27 hPa	30°C / 75% RH	30°C ± 2°C / 75% RH ± 5% RH	40°C ± 2°C / 75% RH ± 5% RH

* GT = greater than (>); LT = less than (<); NMT = not more than (≤).

finished product. Test procedures used in stability testing must be validated and be stability indicating. Stability samples should be stored in container-closure systems that simulate the packaging proposed to distribute the finished UNIMMAP-MMS product for consumer/patient use. Stability studies should include testing of those attributes of the dietary supplement that are susceptible to change during storage and that influence the quality of the dietary supplement.

The first three (3) production batches should be placed on the stability monitoring program to establish the product shelf life (expiration) date. The lots should be those that are manufactured at the regular manufacturing scale; however, two of the three production batches can be at least 1/10th the size of the manufacturing scale. Thereafter, at least one (1) batch per year of manufactured UNIMMAP-MMS product should be added to the stability monitoring program. All batches must comply with the finished product specification throughout the product shelf life (expiration) date.

As appropriate, the stability storage conditions for temperature and relative humidity (RH) for product that is intended for use globally should be for Climatic Zone IVb, hot and very humid. However, actual climatic conditions in the country of destination of the UNIMMAP-MMS product may require stability studies to be carried out under the conditions of a different climatic zone (e.g., Climatic Zone III, hot and dry). **Table 2** shows the recommended testing conditions appropriate to each climatic zone that might be required in a given country of destination of the product.

The frequency of testing should be sufficient to establish the stability profile of the dietary supplement. The storage conditions and length of studies chosen should be sufficient to cover storage, shipment, and subsequent use. Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions, such as might occur during shipping. The shelf life (expiry) period of the UNIMMAP-MMS should be 30 months, at minimum. The following testing frequencies are recommended:

- Long term = 0, 3, 6, 9, 12, 18, 24, 30, and 36 months; and
- Accelerated = 0, 3, and 6 months.

Where an expectation (based on development experience) exists in consequence of accelerated studies that are likely to approach significant change criteria, increased testing should be conducted by adding samples at the 1-month and 2-month time points. In general, a significant change for a dietary supplement is defined as a 5% change in the assay from its initial value, or failure to meet any of its product specification acceptance criteria.

4 Packaging

4.1 Package types and tablet count

This specification focuses on the use of UNIMMAP-MMS product packaged in bottles containing 180 tablets per bottle. Bottles (or blister packaging) containing 30 tablets are acceptable, but packaging options/tablet counts should be considered in light of cost and environmental implications, and evidence that may come later as to the impact that a particular packaging option or tablet

count may have on distribution, uptake, adherence rates, or clinic attendance.[4]

Bulk packaging for business-to-business transactions is acceptable, with demonstrated stability. Bulk packaging for clinics (e.g., bottles containing 500, 1,000, etc. tablets) should be avoided due to health and safety concerns to avoid inadvertent child exposure to the UNIMMAP-MMS product, and to avoid re-packaging by clinic staff of MMS into other temporary, less desirable packaging (e.g., plastic bags and newspaper), which may cause premature product deterioration.

4.2 Bottles

Bottles must be:

- white/opaque;
- screw-cap;
- high-density polypropylene (HDPE) material (complying with internationally recognized pharmacopoeia standards);
- tamper-evident; and
- child-resistant.

The need for desiccant depends on tablet formulation, and must be determined by the manufacturer based on experience and supporting stability data.

4.3 Blister packaging

If blister packaging is used, a thermoformable moisture barrier film, such as Aclar®, should be used to ensure stability of the product throughout the shelf life of the product. Using a child-resistant version of a blister pack is deemed impractical as the 'child-resistant' requirement makes it unusually difficult to dispense the pack's contents.

4.4 Labeling

Labeling must comply with applicable country of destination regulatory requirements for the food/dietary/nutritional supplement.

Quantitative label claims for the product must be truthful and accurately reflect the contents of the declared food/dietary/nutritional ingredients; fortified or fabricated nutrients must meet 100% of the quantitative label claim throughout the shelf life of the product for products that can be distributed within the USA. For products distributed outside the USA, fortified or fabricated nutrients must meet USP compendial assay acceptance criteria (see section 6.2 for details.)

The UNIMMAP-MMS product label should list:

- the term "food supplement", "dietary supplement", or "nutritional supplement";
- the quantity of each dietary ingredient and the correct reference daily intake, listed as % Daily Value, as necessary; and
- the common or usual name of each ingredient in descending order of predominance by weight, with the exception that dietary ingredients listed in the nutrition label supplement facts need not be repeated in the ingredient list; incidental additives including water, present in a dietary supplement at insignificant levels, are exempted from this requirement.

Labels for the UNIMMAP-MMS product containing iron or iron salts for use as an iron source must include the following required cautionary statement: "WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately."

The label must include a statement of the necessary storage requirements for the UNIMMAP-MMS product. The label must accurately state the country of origin for any product of foreign origin imported into the country of destination.

The name and place of business of the manufacturer, packer, or distributor, and the expiration date must be located to the right of the principal display panel. When the name appearing on the label is not that of the actual manufacturer, the name should be qualified in a manner that accurately reflects this relationship (e.g., "Manufactured for __", "Distributed by __"). The label must include a domestic address or phone number through which an adverse event report for a dietary supplement may be received (see **Figure 1**).

5 Manufacturing standards and certificates

5.1 Pharmacopoeia standards

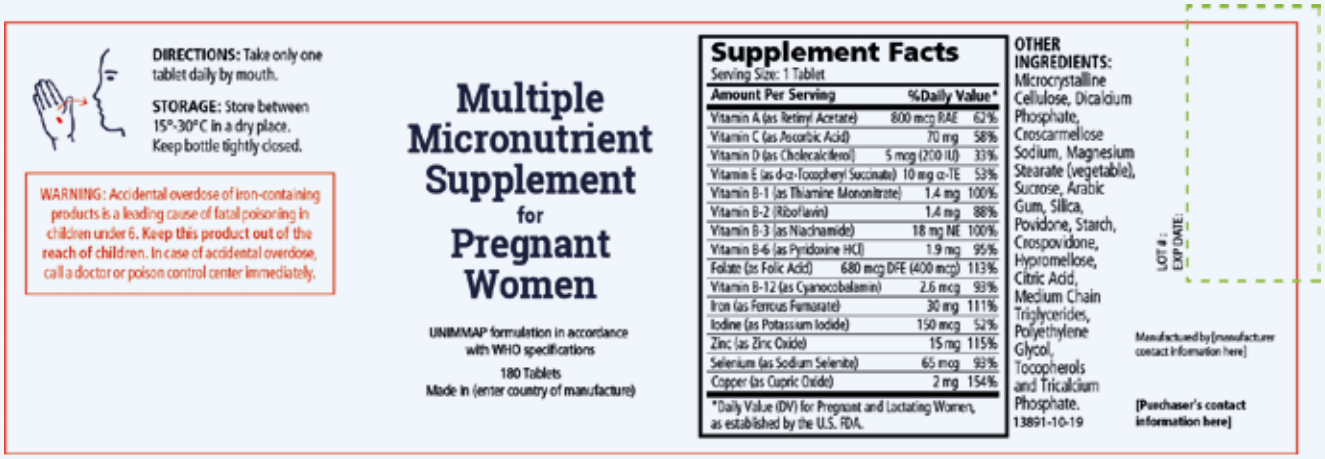
Compliance to the following international pharmacopoeial standards is acceptable for food/dietary/nutritional supplement ingredients and finished product:

1. United States Pharmacopeia *(USP)*
2. European Pharmacopoeia *(Ph. Eur.)*
3. International Pharmacopoeia *(Ph. Int.)*
4. British Pharmacopoeia *(BP)*
5. Japanese Pharmacopoeia *(JP)*

5.2 Manufacturing practices and conditions

The UNIMMAP-MMS product must be manufactured under current Good Manufacturing Practice (cGMP) regulations promulgated by an internationally recognized regulatory authority (e.g.,

FIGURE 1: Cost-effectiveness of MMS in South Africa



the United States Food and Drug Administration [US FDA], the Medicines and Healthcare products Regulatory Agency [MHRA], or other GMP guidelines issued by a stringent authority (e.g., the World Health Organization [WHO]), by a Pharmaceutical Inspection Co-operation Scheme (PIC/S) member, or by a globally recognized pharmacopoeia (e.g., USP), including but not limited to:

- US FDA 21 CFR Part 111 *Current Good Manufacturing Practice in Manufacturing, Packing, Labeling, or Holding Operations for Dietary Supplements;* and
- *USP–NF general chapter* (2750) *Manufacturing Practices for Dietary Supplements.*

The manufacturing site and operations should be audited by an accredited third-party certification body.

5.3 Certificates of Analysis

A Certificate of Analysis (CoA) must be issued for each batch of the UNIMMAP-MMS product. The CoA should list the name and item code of the UNIMMAP-MMS product, the batch number, the date tested and released, and the expiry date. The CoA should list each test performed, the specific identity of the test procedure, the acceptance limits or criteria, and the results with numerical units, as appropriate. The CoA should be dated and signed by authorized quality unit personnel. When issued for external use, the CoA should list the name, address and telephone number of the manufacturer.

The testing protocol should include the performance of full specification testing. However, a reduced level of testing (or sampling) for particular specified parameters may be allowed based upon one or more of the following: statistical analysis of an adequate quantity of historical test data, statistical confidence in the capability of the manufacturing process as determined by suitable verification, or ongoing monitoring of the process using recognized statistical process control (SPC) techniques. The manufacturer must notify the purchaser of the UNIMMAP-MMS product in writing of any change to the testing protocol.

5.4 Halal certification

The UNIMMAP-MMS product may be manufactured to meet Halal requirements. The exact requirements must be obtained from local authorities or from an accredited source.

5.5 Change control

A manufacturer might make changes to the UNIMMAP-MMS product's specification, raw material source, manufacturing processing steps and/or equipment, testing protocols, or any other criteria deemed by the participant to be essential or significant to product quality. Manufacturers must notify the purchaser of the UNIMMAP-MMS product of any significant changes that might affect product quality, in writing upon implementation, along with the rationale for the change(s).

A manufacturer must also notify the purchaser of the UNIMMAP-MMS product of any change to its manufacturing site, including any changes to the certification status held by the manufacturer from a GMP issuing authority.

5.6 Quality agreement

There should be a written and approved contract or quality agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party. The contract should permit the purchaser to audit the manufacturer's (seller's) facilities for compliance with GMPs. Where subcontracting is allowed, the seller should not pass to a third party any of the work entrusted to it under the contract without the buyer's prior evaluation and approval of the arrangements.

TABLE 3: Tablet characterization and purity

Test	Test method	Acceptance criteria
Physical characteristics		
Appearance	Visual	TBD by manufacturer
Shape	Visual	TBD by manufacturer
Tablet thickness	Micrometer	TBD by manufacturer
Tablet length	Micrometer	TBD by manufacturer
Tablet friability	USP ‹1216›	TBD by manufacturer
Tablet breaking force	USP ‹1217›	TBD by manufacturer
Performance		
Average tablet weight	USP ‹2091›	TBD by manufacturer
Weight variation		Each of the individual weights is within 95%–105% of the average weight
Dissolution for vitamin A (index for oil-soluble vitamins)	USP ‹2040› Apparatus 2, at 75 rpm, in 0.05 M phosphate buffer pH 6.8, w/ 1% (w/v) sodium ascorbate and 1% (w/v) octoxynol 9, 900 mL	NLT 75% of the labeled amount of vitamin A dissolved in 45 minutes
Dissolution for folic acid	USP ‹2040 Apparatus 2, at 75 rpm, in water or 0.05 M pH 6.0 citrate buffer, 900 mL	NLT 75% of the labeled amount of folic acid dissolved in 1 hour
Dissolution for riboflavin (index for water-soluble vitamin)	USP ‹2040› Apparatus 2, at 75 rpm, in 0.1 N hydrochloric acid, 900 mL	NLT 75% of the labeled amount of riboflavin dissolved in 1 hour
Dissolution for iron (index element)		NLT 75% of the labeled amount of iron dissolved in 1 hour
Elemental impurities		
Arsenic (inorganic)	USP ‹233› & USP ‹2232›	NMT 15 mcg/day
Cadmium		NMT 5 mcg/day
Lead		NMT 5 mcg/day
Mercury (total)		NMT 15 mcg/day
Methylmercury (as Hg)*		NMT 2 mcg/day
Microbial contaminants		
Total aerobic microbial count (TAMC)	USP ‹2021›	NMT 3×10^3 CFU/g
Total combined yeast & mold (TCYM)	USP ‹2021›	NMT 3×10^2 CFU/g
Absence of *Escherichia coli*	USP ‹2022›	Absent in 10 g
Absence of *Salmonella spp.*	USP ‹2022›	Absent in 10 g
Absence of *Staphylococcus aureus*	USP ‹2022›	Absent in 10 g
Enterobacterial count (bile-tolerant Gram-negative bacteria)	USP ‹2021›	NMT 10 CFU/g

CFU = colony-forming unit; **NLT** = not less than (≥); **NMT** = not more than (≤); **USP ‹233›** Elemental impurities – Procedures; **USP ‹2232›** Elemental contaminants in dietary supplements; **USP ‹2021›** Microbial enumeration tests – Nutritional and dietary supplements; **USP ‹2022›** Microbiological procedures for absence of specified microorganisms – Nutritional and dietary supplements.* Methylmercury determination is not necessary when the content of total mercury is less than the limit for methylmercury.

6 Finished product specification

UNIMMAP is a formulation for use by pregnant women. The UNIMMAP-MMS formulation was developed during a workshop of experts organized by the World Health Organization (WHO), UNICEF, and the United Nations University in 1999 specifically to identify an MMS formula for efficacy clinical trials. It contains 15 micronutrients at dosages that approximate the recommended dietary allowances for pregnancy.

The criteria and requirements for tablet characterization and purity are shown in **Table 3**, and the potency assay requirements are shown in **Table 4**.

7 Analytical test methods

Tests and examinations that are used to determine whether the UNIMMAP-MMS product specification is met must be appropriate for their intended use, and scientifically validated methods. Test

methods or procedures must meet proper standards of accuracy and reliability.

If the test procedure is not in an official compendium, the procedure must be validated according to USP general chapter ‹1225› *Validation of Compendial Procedures*, or ICH Q2(R1) *Validation of Analytical Procedures: Text and Methodology*. Method performance characteristics include specificity, linearity, range accuracy, precision, detection limit, and quantitation limit; and those of interest may vary depending on the type of test: identification, assay, impurities, or performance.

If the test procedure is in an official compendium, such as the *USP–NF*, the procedure only needs to be verified for its suitability under actual conditions of use, according to USP general chapter ‹1226› *Verification of Compendial Procedures*. Verification requirements should be based on an assessment of the complexity of both the procedure and the material to which the procedure is applied. Verification is not required for basic compendial procedures, such as loss on drying or residue on ignition, and simple instrumental determinations, such as pH measurements.

An alternative method or procedure is defined as any method or procedure other than the compendial method or procedure for the article in question. The alternative method or procedure must be fully validated and must produce comparable results to the compendial method or procedure within allowable limits estab-

TABLE 4: Potency assay requirements (per tablet)

Ingredient	Test method*	Label claim	USP	US FDA**
Vitamin A	Vitamin A,	800 mcg	NLT 90.0%	NLT 100.0%
(as retinyl acetate)	Method 1		NMT 165.0%	NMT 175.0%
Vitamin C	Vitamin C assay	70 mg	NLT 90.0%	NLT 100.0%
(as ascorbic acid)	‹580›, Method 2		NMT 150.0%	NMT 160.0%
Vitamin D	Cholecalciferol or	5 mcg	NLT 90.0%	NLT 100.0%
(as cholecalciferol)	ergocalciferol, Method 1	(200 IU)	NMT 165.0%	NMT 175.0%
Vitamin E (as dl-alpha	Vitamin E,	10 mg	NLT 90.0%	NLT 100.0%
tocopheryl succinate)	Method 1		NMT 165.0%	NMT 175.0%
Vitamin B_1: thiamine		1.4 mg	NLT 90.0%	NLT 100.0%
(as thiamine mononitrate)			NMT 150.0%	NMT 160.0%
Vitamin B_2:	Niacin or niacinamide,	1.4 mg	NLT 90.0%	NLT 100.0%
riboflavin	pyridoxine hydrochloride,		NMT 150.0%	NMT 160.0%
Vitamin B_3: niacin	riboflavin and thiamine,	18 mg	NLT 90.0%	NLT 100.0%
(as niacinamide)	Method 1		NMT 150.0%	NMT 160.0%
Vitamin B_6:		1.9 mg	NLT 90.0%	NLT 100.0%
pyridoxine hydrochloride			NMT 150.0%	NMT 160.0%
Folate	Folic acid,	680 DFE	NLT 90.0%	NLT 100.0%
(as folic acid)	Method 1	(400 mcg folic acid)	NMT 150.0%	NMT 160.0%
Vitamin B_{12}:	Cyanocobalamin,	2.6 mcg	NLT 90.0%	NLT 100.0%
(as cyanocobalamin)	Method 1		NMT 150.0%	NMT 160.0%
Iodine	Iodide	150 mcg	NLT 90.0%	NLT 100.0%
(as potassium iodide)			NMT 160.0%	NMT 170.0%
Iron		30 mg	NLT 90.0%	NLT 100.0%
(as ferrous fumarate)	Copper, iron,		NMT 125.0%	NMT 135.0%
Zinc	and zinc, Method 2;	15 mg	NLT 90.0%	NLT 100.0%
(as zinc oxide)	selenium, Method 3;		NMT 125.0%	NMT 135.0%
Selenium	plasma spectrochemistry	65 mcg	NLT 90.0%	NLT 100.0%
(as sodium selenite)	‹730›		NMT 160.0%	NMT 170.0%
Copper		2 mg	NLT 90.0%	NLT 100.0%
(as cupric oxide)			NMT 125.0%	NMT 135.0%

NLT = not less than (≥); **NMT** = not more than (≤).
***** All tests to be performed per current USP–NF Oil- and Water-Soluble Vitamins with Minerals Tablets.
****** USP General Notices 4.10.20. Acceptance Criteria: An official product shall be formulated with the intent to provide 100% of the quantity of each ingredient declared on the label. Where the minimum amount of a substance present in a dietary supplement is required by law to be higher than the lower acceptance criterion allowed for in the monograph, as per 21 CFR 101.36(f)(1) and 21 CFR 101.9(g)(3) and (g)(4), the upper acceptance criterion in the monograph may be increased by a corresponding amount.

TABLE 5: Definitions and acronyms

Term / abbreviation	Definition / long form
Accredited third-party certification body	An accredited third-party certification body means a third-party certification body that meets the applicable requirements of ISO/IEC 17020:2012 and/or ISO/IEC 17065:2012, and is accredited to conduct audits or inspections according to the applicable standard or regulatory requirements.
Article	Article includes substances (such as excipients, food/dietary/nutritional ingredients, in-process material), products (such as food/dietary/nutritional supplements), and materials (such as packaging containers and closures, and labels).
Batch	Batch is a specific quantity of a food/dietary/nutritional supplement or other article that is: intended to be uniform; intended to meet specifications for identity, purity, strength, and composition; and produced during a specified time period according to a single manufacturing record during the same cycle of manufacture.
CFR – Code of Federal Regulations (CFR)	A CoA is a document relating specifically to the results of testing a representative sample drawn from a batch of material. The CoA should list each test performed in accordance with compendial or manufacturer requirements, including reference to the test procedure, the acceptance limits, and the results obtained.
Composition	Composition is the specified mix of food/dietary/nutritional ingredients and excipients in a food/dietary/ nutritional supplement.
Country of destination	The country in which the product is intended to be marketed/ used.
Excipients	Excipients are substances other than food/dietary ingredients that have been appropriately evaluated for safety and are intentionally included in a food/dietary supplement to do one or more of the following: aid in the manufacture of a food dietary supplement; protect, support, or enhance stability, bioavailability, or user acceptability; assist in product identification; and/or enhance any other attribute of the overall safety or delivery of the food/dietary supplement during storage or use. The term excipient is sometimes used synonymously with the term inactive ingredients and other ingredients.
Food/dietary/nutritional ingredient	Food/dietary/nutritional ingredients are ingredients with an established nutritional value, namely vitamins and minerals in their respective chemical entity.
Food/dietary/nutritional supplement	A food/dietary/nutritional supplement is a product intended to supplement the diet that: contains one or more food dietary/nutritional ingredients; is intended for ingestion in a tablet, capsule, or liquid form; is not represented for use as a conventional food or as the sole item of a meal or the diet; is labeled as a food/dietary/nutritional supplement; and is sometimes referred to as a multiple micronutrient supplement (MMS).
Food/dietary/nutritional supplement ingredient	A food/dietary/nutritional supplement ingredient includes food/dietary ingredients and excipients.
Globally recognized pharmacopoeia compendial standard	The following international pharmacopoeia's official compendial standards are considered globally recognized: 1. British Pharmacopoeia (BP) 2. European Pharmacopoeia (Ph. Eur.) 3. International Pharmacopoeia (Ph. Int.) 4. Japanese Pharmacopoeia (JP) 5. United States Pharmacopeia (USP)
GMP and cGMP – Good Manufacturing Practices and current Good Manufacturing Practices	Good manufacturing practices and current good manufacturing practices as promulgated by an internationally recognized regulatory authority (e.g., US FDA, MHRA), or other GMP guidelines as promulgated by a stringent authority (e.g., WHO), a by Pharmaceutical Inspection Co-operation Scheme member (e.g., PIC/S), or by a globally recognized pharmacopeia (e.g., USP).
ICH or International Council for Harmonisation of Technical Requirements Pharmaceuticals for Human Use; and ICH Q1A and ICH Q1 R1	The *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).* ICH brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration **and:** • *Stability Testing of New Drug Substances and Drug Products (ICH Q1A)* • *Validation of Analytical Procedures: Text and Methodology (ICH Q2(R1))*
MHRA	Medicines and Healthcare products Regulatory Agency.
MNF – Micronutrient Forum	The Micronutrient Forum serves as a global catalyst and convener for sharing expertise, insights and experience relevant to micronutrients in all aspects of health promotion and disease prevention, with special emphasis on the integration with relevant sectors.

Definitions and acronyms

Term / abbreviation	Definition / long form
Not less than (NLT)	NLT is equal to, but not less than, a given value.
Not more than (NMT)	NMT is equal to, but not more than, a given value.
Pharmaceutical Inspection Co-operation Scheme (PIC/S)	PIC/S is a non-binding, informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. PIC/S currently consists of 52 participating authorities and aims at harmonizing inspection procedures.
To be determined (TBD)	TBD describes a variable that has not yet been determined.
UNIMMAP – United Nations International Multiple Micronutrient Antenatal Preparation	UNIMMAP is a formulation for a prenatal micronutrient supplement intended for use in developing countries that was developed in 1999 by UNICEF, the United Nations University (UNU), and the World Health Organization (WHO). It contains 15 micronutrients at dosages that approximate the recommended dietary allowances for pregnancy.
USFDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
VAA – Vitamin Angel Alliance	The Vitamin Angel Alliance, Inc. is a 501(c)(3) tax-exempt 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. Vitamin Angels focuses on filling gaps in coverage for interventions that target the first 1000 days of life (i.e., from conception through 24 months of age) and children up to 5 years of age. (www.vitaminangels.org).

lished on a case-by-case basis. Alternative methods or procedures can be developed for any number of reasons not limited to simplification of sample preparation, enhanced precision and accuracy, improved (shortened) run time, or being better suited to automation than the compendial method or procedure. Only those results obtained by the methods and procedures given in the compendia are conclusive.

8 Storage and transportation requirements

The UNIMMAP-MMS product must be held under appropriate conditions of temperature, humidity, and light so that its identity, purity, strength, and composition are not affected (e.g., not less than 15°C and not more than 30°C, protected from humidity and light).

The UNIMMAP-MMS product must be distributed under conditions that will protect it against contamination and deterioration. The manufacturer and purchaser need to work together to ensure this requirement is met.

All transportation operations must be conducted under such conditions and controls necessary to prevent the UNIMMAP-MMS product from becoming adulterated during transportation. Responsibility for ensuring that transportation operations are carried out adequately must be assigned to competent supervisory personnel. Shippers, receivers, loaders, and carriers engaged in transportation must conduct all transportation operations under such conditions and controls necessary to protect the UNIMMAP-MMS product from becoming adulterated during transportation. These operations include, but are not limited to, taking effective measures such as:

- segregation, isolation, or the use of packaging to protect the UNIMMAP-MMS product from contamination from other articles in the same load;
- use of vehicles and transportation equipment that are adequately designed and maintained in a sanitary condition to prevent the UNIMMAP-MMS product from becoming contaminated during transportation operations; and
- use of vehicles and transportation equipment that are adequately designed, maintained, and equipped to transport the UNIMMAP-MMS product under adequate temperature and humidity control to prevent the UNIMMAP-MMS product from becoming adulterated during transportation.

The first manufactured batch of the UNIMMAP-MMS product should be distributed first. Distributing operations must be designed to facilitate its recall, if necessary.

9 Definitions and acronyms

see **Table 5**.

10 End/technical notes

[1] The consensus open-access UNIMMAP-MMS product specification presented here 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 (NYAS) Multiple Micronutrient Supplementation Technical Advisory Group (MMS TAG) and the Micronutrient Forum (MNF), with funding from the Bill & Melinda Gates Foundation. This document is re-formatted from the version published in the New York Academy of Sciences.[1] For more information or assistance in understanding how to apply this product specification, contact the New York Academy of Sciences MMS TAG, the Micronutrient Forum, or the Vitamin Angel Alliance. Technical Consultation participants included:

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- Nita Dalmiya, UNICEF (observer)**
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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 an 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.

[2] This specification states a preference for a film-coated tablet, which provides certain benefits including lower cost and better performance and stability under expected conditions of high temperature and humidity. However, capsules that demonstrate equal or better performance may also be considered.

[3] Readers should consider the following:

- The UNIMMAP–MMS product might be considered a medicinal product in some countries, and if so, the product must comply with the respective regulatory requirements of that country.
- No reference is made in this document to 'pharmaceutical' or 'medicinal' ingredients or products, although the product might be considered a medicinal product in some countries.
- This specification outlines the minimum requirements for the manufacture of a UNIMMAP–MMS product; as previously indicated, if a country has stricter requirements, they must be met.

[4] No evidence exists in the literature to indicate that a bottle or blister pack containing 30 tablets increases uptake or adherence rates, or clinical attendance. Additionally, both a 30-count bottled product and a 30-count blister pack product are considerably more expensive to produce and have a greater environmental impact burden than a 180-count bottled product. For these reasons, the 180-count, HDPE bottled product was selected as the preferred packaging option. If future implementation research shows otherwise, other packaging options may be considered with.

Reference

[1] Multiple Micronutrient Supplement Technical Advisory Group (MMS-TAG), Micronutrient Forum (MNF). Expert consensus on an open-access United Nations International Multiple Micronutrient Antenatal Preparation-multiple micronutrient supplement product specification. Annals of the New York Academy of Sciences. 2020 Mar DOI: 10.1111/nyas.14322. Internet: https://www.nyas.org/media/21537/expert-consensus-on-an-open-access-unimmap-mms-prod-spec.pdf (Accessed 27 April, 2020)"

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