



Understanding Product Quality As Applied to UNIMMAP–MMS Product Donated by Kirk Humanitarian

John B. Atwater, Ph.D. | September 2020

Key Takeaway Messages

1. Currently, the only publicly available product specification for use by purchasers and manufacturers of a United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP)—multiple micronutrient supplement (MMS) product—is the Expert Consensus *UNIMMAP–MMS Product Specification*.
2. A major challenge when discussing the quality of a manufactured UNIMMAP–MMS product is that there is little consensus on how a nutritional product is classified in different countries or by international agencies; it can be considered either a dietary supplement regulated as a food or a therapeutic product regulated as a drug.
3. When anticipating a UNIMMAP–MMS product to be acceptable to public health nutrition programs around the world in which the nutritional product might be manufactured globally, the *Expert Consensus UNIMMAP–MMS Product Specification* established that the product must conform to a combination of internationally recognized GMP requirements and/or guidelines for nutritional products, and internationally recognized pharmacopeial quality standards for a nutritional product.
4. Kirk Humanitarian’s UNIMMAP–MMS product conforms to the *Expert Consensus UNIMMAP–MMS Product Specification* which is based primarily on reference to the United States Pharmacopeia (USP) quality standards that are critical to ensuring the safety and purported benefits of both dietary supplements and drug products, and it is manufactured in a facility that meets US FDA cGMP and USP GMP requirements for nutritional products (i.e., dietary supplements).
5. Kirk Humanitarian requires that its contract manufacturers participate in the USP Dietary Supplement Verification Program (DSVP), which provides credible, trustworthy, third-party assurance that their US-manufactured products comply with US FDA cGMP requirements and with USP quality standards.
6. The quality of Kirk Humanitarian’s USP Verified UNIMMAP–MMS product is comparable to that for a drug product and complies with UNICEF’s technical requirements for both pharmaceutical and food nutritional products. That comparison is possible due to the manufacturers’ participation in the USP DSVP, which requires compliance not only to the USP FDA cGMPs in 21 CFR 111, but also to USP’s more rigorous, drug-like manufacturing requirements in general chapter <2750>.

1. Introduction

The purpose of this document is to provide a detailed explanation of the technical standards to which the Kirk Humanitarian (KH) United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP)—Multiple Micronutrient Supplement (MMS) product conforms, in order support a statement of comparability between KH’s product and that offered by UNICEF. Kirk Humanitarian’s UNIMMAP–MMS product conforms to the *Expert Consensus UNIMMAP–MMS Product Specification*^{1,2}, and is manufactured according to both the United States Food and Drug Administration (US FDA) current Good Manufacturing Practices (cGMPs) for dietary supplements and the United States Pharmacopeia (USP) quality standards for the manufacture of dietary supplements. Kirk Humanitarian requires that its contract manufacturers participate in the USP Dietary Supplement Verification Program (DSVP) to provide credible, trustworthy, third-party assurance that their US–manufactured products comply with US FDA and USP GMP requirements, and with USP quality standards and other DSVP requirements. Products manufactured outside the US may use other globally recognized GMPs and pharmacopeial standards as required and specified in the *Expert Consensus UNIMMAP–MMS Product Specification*. Use of the USP DSVP provides a high level of confidence that the quality of Kirk Humanitarian’s manufactured UNIMMAP–MMS product will be comparable to that for a drug product and will comply with UNICEF’s technical requirements for nutritional products.

2. Understanding the Terminology: Nutritional Supplements–Drug Product or Dietary Supplement

A major challenge when discussing the quality of a manufactured UNIMMAP–MMS product (which will be referred to throughout this paper as simply a “nutritional supplement”) is that there is little consensus on the terminology, definition, and requirements by which such a product is classified in different countries or by international agencies. Quality requirements for the manufacture of nutritional supplements are controlled through pharmacopeial standards and good manufacturing practices (GMPs) enforced by each national regulatory authority. Both pharmacopeia quality standards and GMPs may vary in different countries or regions. **Table 1** briefly describes the regulatory framework for the manufacture of nutritional supplements in different countries. As shown in Table 1, nutritional supplements can be considered a dietary supplement regulated as a food or a therapeutic product regulated as a drug. Regulatory agencies and international agencies around the world, including the United States Food and Drug Administration (US FDA), Health Canada (HC), the Australian Therapeutics Goods Administration (TGA), and the World Health Organization (WHO), set different GMP requirements and/or guidelines for the manufacture of nutritional products. Also, pharmacopeias around the world, including the *United States Pharmacopeia (USP)*, the *European Pharmacopeia (Ph. Eur.)*, *British Pharmacopeia (BP)*, *Japanese Pharmacopeia (JP)* and the *International Pharmacopeia (Ph. Int.)*, establish quality standards for nutritional supplements which are not always harmonized. This lack of harmonization can present challenges when a nutritional supplement is imported into countries with different levels of regulations. Harmonization on the regulatory requirements of drug products is common, primarily by the International Conference on Harmonization (ICH), but such an effort is lacking for nutritional supplements. To suggest that one approach or combination thereof is better than another can be a subjective argument. Most, if not all, of the countries listed in Table 1 have regulatory authorities for medicines that are considered stringent regulatory authorities (SRAs) by WHO, based on an interim definition of SRA.

¹ Expert Consensus on an Open-Access Product Specification for MMS for Pregnant Women, Special Report: Focusing on Multiple Micronutrient Supplements in Pregnancy. Sight and Life, April 2020. Available at: https://sightandlife.org/wp-content/uploads/2020/04/SightandLife_SpecialReport_ExpertMMS_.pdf

² 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, Special Issue: Annals Reports, Technical Report, ISSN 0077-8923. First published March 9, 2020. Available at: <https://doi.org/10.1111/nyas.14322>. The consensus open-access UNIMMAP – MMS product specification referenced here for download was produced for global use by a technical consultation of experts convened in Washington D.C. on 11-12 November 2019, and hosted jointly by the New York Academy of Science’s Multiple Micronutrient Supplementation Technical Advisory Group (MMS-TAG) and the Micronutrient Forum with funding from the Bill & Melinda Gates Foundation. UNICEF participated in the Technical Consultation, but its role 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 to deliver 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.

TABLE 1. Product terminology/classification and GMP requirements for “nutritional supplements” by different regulatory and international agencies around the world.

COUNTRY OR ORGANIZATION	REGULATORY AUTHORITY	PRODUCT CLASSIFICATION FOR NUTRITIONAL SUPPLEMENTS ¹	PRODUCT NAME(S)	GMP REQUIREMENTS	RECOGNIZES USP STANDARDS ²
Australia	Therapeutic Goods Administration (TGA)	Medicine (Drug)	Complementary Medicine	PIC/S Guide to Good Manufacturing Practice (GMP) – 01 July 2018, PE009-14, except Annexes 4, 5 & 14	Yes
Canada	Health Canada (HC)	Therapeutic Product (Drug)	Natural Health Product	Natural Products Regulations SOR 2003-196, Part 3 Good Manufacturing Practices	Yes, Official
China	State Administration for Market Regulation (SAMR)	Health Food	Health Functional Food	SAMR regulation (currently in draft)	Yes
EU	European Food Safety Authority (EFSA) Competent Authority of Member States	Food	Food Supplement	Food Supplements Europe Guide to GMP for Manufactures of Food Supplements	Yes, Official
India	Food Safety and Standards Authority of India (FSSAI)	Food	Functional Food Nutraceutical Health Supplement	FSSAI Guidance Document: Food Safety Management Systems	Yes, Official
Japan	Ministry of Health, Labor and Welfare (MHLW) for Medicines Consumer Affairs Agency (CAA) for Supplements	Food	Food with Health Claim	MHLW Food Sanitation Law Article 11 GMP & Japan Health and Nutrition Food Association (JHNFA) GMP or Japanese Institute for Health Food Standards (JIHFS) GMP	No
Korea	Ministry of Food and Drug Safety (MFDS) and Korean Food and Drug Administration (KFDA)	Food	Health Functional Food	Enforcement Rule, Article 26 of the Health Functional Food Act, Article 22	Yes
Mexico	Federal Commission against Sanitary Risk (COFEPRIS)	Medicines	Vitamin Medication	Federal Law of Metrology and Normalization – Normas Oficial Mexicanas NOM-059-SSA1-2013	Yes
New Zealand	Medicines and Medical Devices Safety Authority (Medsafe)	Drug	Natural Health Product Complementary Medicine Dietary Supplement	New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods	Yes
South Africa	South African Health Products Regulatory Authority (SAHPRA)	Foodstuff	Health Supplements	4.01 Guide to GMP for Medicines in SA: PIC/S Guide to GMP	Yes
World Health Organization (WHO)	Standards and Scientific Advice on Food and Nutrition (SSA)	Medicine	Nutritional Supplements	Annex 2: WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles & Annex 7: Application of HACCP Methodology to Pharmaceuticals	Yes

COUNTRY OR ORGANIZATION	REGULATORY AUTHORITY	PRODUCT CLASSIFICATION FOR NUTRITIONAL SUPPLEMENTS ¹	PRODUCT NAME(S)	GMP REQUIREMENTS	RECOGNIZES USP STANDARDS ²
United Nations Children’s Fund (UNICEF)	Regulatory Authority in the Country of Manufacturer	Food or Drug	Nutritional Product	Codex Alimentarius CAC/GL 55 – 2005 or Relevant Pharmacopeia	Yes
United States	Food and Drug Administration (FDA) Office of Dietary Supplement Programs	Food	Dietary Supplement	21 CFR part 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements	Yes, Official

TABLE 1 NOTES:

¹ Nutritional supplements means dietary supplements containing only vitamins and minerals as dietary ingredients.

² Yes means USP–NF standards are used in the country in an unofficial capacity, e.g., recognized along with other international pharmacopeia standards secondarily if a monograph does not exist in the country’s national pharmacopeia, or in general practice; Official means USP–NF standards are legally recognized in a statute; No means that no use of USP–NF standards or other international pharmacopeia standards is implicitly implied.

An organization might claim that a product is “pharmaceutical grade,” however, there is no official definition for the term “pharmaceutical grade.” It is a marketing term that can have different meanings for different countries/ companies/individuals. Some might consider it to mean that the product was made according to a particular set of GMP requirements and/or a particular set of pharmacopeial standards. Others might consider it to mean that an official regulatory authority has approved the product for market distribution as a drug product. In some cases, such as in the United States, a dietary supplement and a drug product can be made to the same USP quality standards, but be marketed differently based on the quantity of the dietary ingredient or active pharmaceutical ingredient (e.g., Folic Acid) and/or the health claim(s) made on the product label. It is the intended use that often determines whether a product is a dietary supplement or drug product. This brief is intended to show how Kirk Humanitarian’s UNIMMAP–MMS product is made to the same quality standards whether it would be considered a dietary supplement or a drug product in the United States.

3. What Drives Problems with Product Quality in the Absence of Verification

Often quality problems are created by price competition and the lack of product differentiation. Nutritional supplement purchasers are often unwilling to pay a premium for a quality product, and manufacturers attempt to minimize expenditures where possible. These two economic incentives create a conflict between product quality and a manufacturer's profit margin. Nutritional supplement purchasers are not always attuned to differences in the quality of manufactured products due to their limited ability to accurately assess nutritional supplements' production quality. They may consider product manufactured according to a given set of regulatory requirements and pharmacopeial standards as equivalent; however, that is not always the case. Compliance to pharmacopeial standards (see **Box 1** for a description of USP Quality Standards) and GMP regulations (see **Box 2** for a description of Good Manufacturing Practices for Nutritional Supplements in the United States) can be interpreted incorrectly and/or incompletely (see **Box 3** for a comparison of Dietary Supplement GMPs versus Drug Product GMPs in the United States). Use of an independent, third-party certification program, such as the USP DSVP can provide assurance that a manufactured product complies with regulatory and quality standards (see **Box 4** for more information about regulatory inspections and audits: Understanding Regulatory Inspections/Audits).

BOX 1. USP QUALITY STANDARDS

The United States Pharmacopeial Convention (USPC) establishes public quality standards for drugs, dietary supplements, and foods. Use of USP public standards—public specifications containing tests, procedures, and acceptance criteria—in conjunction with current Good Manufacturing Practices (cGMPs) help ensure the quality and consistency of nutritional products. USP standards for identity, strength, and purity, with limits on contaminants, are generated through a credible, science-based process by independent experts serving on the Council of Experts. USP standards are generally made available to the public for comment prior to finalization, and when finalized, are available publicly.

USPC publishes two compendia in a single volume: the United States Pharmacopeia (USP) and the National Formulary (NF). NF contains monographs for pharmaceutical excipients, and USP contains monographs for active pharmaceutical ingredients, drug products, dietary ingredients, dietary supplements, and accompanying general chapters. USPC provides specifications for other ingredients that may be included in a dietary supplement in the Food Chemical Codex (FCC), a compendium of public standards for food ingredients.

A monograph sets out the name and definition of an article (i.e., an ingredient or finished product); any packaging, storage, and labeling requirements, and specifications. The specifications consist of tests necessary to ensure the quality of that ingredient or finished product, one or more analytical procedures for each test, and acceptance criteria that serve as the requirements that the ingredient or finished product must meet to pass the tests. General chapters provide procedures, sometimes with acceptance criteria, that are frequently cited in monographs, or general information such as good manufacturing practices or validation of test procedures.

BOX 2. GOOD MANUFACTURING PRACTICES FOR NUTRITIONAL SUPPLEMENTS IN THE UNITED STATES

FDA dietary supplement cGMPs in 21 CFR part 111 *Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements* provide standards that affect the products, processes, and people involved in dietary supplement manufacturing. These standards support the overall quality of the dietary supplement and include requirements relating to quality management, such as recordkeeping and documentation, staff training, and change control; facility and equipment design, suitability, maintenance, and/or calibration; materials control; production control and packaging and labeling control operations; and laboratory controls. Although in the US dietary supplements are considered a food, they are considered a special type of food that warranted a specific set of GMPs separate from food GMPs in 21 CFR part 117 *Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food*. (Note that Subparts A, B, D, E and F of 21 CFR part 117 also apply to dietary supplements, along with 21 CFR part 111.)

USP general chapter <2750> *Manufacturing Practices for Dietary Supplements* includes all requirements found in the FDA cGMPs in 21 CFR part 111 and 21 CFR part 117 that are applicable to dietary supplements, plus additional requirements for validation of test procedures, finished product performance tests (i.e., dissolution), stability studies, and most importantly, compliance to USP monograph quality standards (which is not necessarily required by law unless the product claims to comply to USP quality standards). The application of USP standards including monograph and general chapters to the manufacture of dietary supplements help ensure the safety and quality of these products for consumers. USP dietary supplement GMP requirements in general chapter <2750> tend to be more drug-like than the food-like requirements in the FDA dietary supplement cGMPs. Because the FDA cGMP regulations must cover every potential dietary ingredient and dietary supplement, they are by necessity general. USP monographs and general chapters are specific to the types of dietary ingredients and dietary supplements and as a result, can control the quality of dietary supplements in a more rigorous and targeted manner.

BOX 3. DIETARY SUPPLEMENT GMPS VERSUS DRUG PRODUCT GMPS IN THE UNITED STATES

GMP regulations are promulgated by various regulatory authorities, and some industry organizations establish their own GMP guidelines, as shown in Table 1. Despite the numerous versions of GMP guidelines, they all have basic requirements for the methods, facilities, and controls used in manufacturing, processing, and packaging of a health product. All GMP guidelines intend to make sure that a product is manufactured using safe, sanitary, well-controlled procedures that help ensure that a product is consistently produced and controlled to the quality standards appropriate for its intended use and as required by the product specification.

All GMPS are open to interpretation, and they are not static. In the US, the FDA interprets the requirements of the Federal Food, Drug and Cosmetic Act and related statutes, including the Public Health Services Act, and promulgates regulations in Title 21 of the Code of Federal Regulations (CFR); and the FDA enforces these regulations. The regulations provide manufacturers with the minimum requirements to be followed for manufacturing and marketing a health product in the US. The GMP requirements are established to be flexible to allow each manufacturer to determine how best to implement the requirements. The FDA also creates guidance documents that represent FDA's current thinking or interpretation on a topic (e.g., Process Validation: General Principles and Practices: Guidance for Industry, 25Jan2011). Guidance documents do not create or confer any official requirement on the manufacturer or FDA; an alternative approach may be used if it satisfies the requirements of the applicable statute and/or regulations.

US FDA GMPS for drugs are codified in 21 CFR part 210 *Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs*, and 21 CFR part 211 *Current Good Manufacturing Practice for Finished Pharmaceuticals*. The US FDA GMPS for dietary supplements are codified in 21 CFR part 111 *Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements*; and the GMPS for foods, in 21 CFR part 117 *Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food*. US FDA GMPS are referred to as "current" GMPS (cGMPS); accordingly, manufacturers are expected to use current technologies and systems that are up-to-date in order to comply with the regulations. The US FDA GMPS for drugs in 21 CFR part 210 and 211 were first promulgated in 1978 and have been amended several times since then; the GMPS for dietary supplements in 21 CFR part 111 and for foods in 21 CFR part 117 were promulgated in 2007 and 2015, respectively.

USP general chapter <2750> *Manufacturing Practices for Dietary Supplements* first became official on May 15, 1993, 14 years before the US FDA cGMPS for dietary supplements. It underwent revisions in 2016 to include additional requirements in the US FDA dietary supplement cGMPS 21 CFR part 111, and is currently undergoing revision to include requirements in the US FDA food cGMPS 21 CFR 117 applicable to dietary supplements, and guidance information on how to comply with certain requirements that are more rigorous than that expected by the US FDA dietary supplement cGMPS and similar to what would be expected for a drug product. USP general chapter <2750> covers a six (6) quality systems approach to GMP compliance and auditing that is similar to that described in the US FDA's *Guidance for Industry; Quality Systems Approach to Pharmaceutical cGMP Regulations*. It covers quality management system, facilities and equipment system, materials system, production system, packaging and labeling system, and laboratory controls system. Consequently, the combination of compliance to USP general chapter <2750> and USP quality standards helps ensure that a dietary supplement will be of equivalent quality to that of a drug product.

BOX 4. UNDERSTANDING REGULATORY INSPECTIONS/AUDITS*

Someone might encounter a health product (i.e., food, dietary supplement, or drug product) manufacturer claiming that their manufacturing operation has been inspected or audited by a regulatory authority, and thus, that they are fully compliant to the applicable regulatory GMP requirements. Such is not necessarily the case. No GMP inspection is the same. GMP inspections can be conducted for a variety of reasons, including an initial inspection for product market approval (which is not required for dietary supplements in the US), or a for-cause inspection to investigate a problem that has been reported to the regulatory authority.

When the US FDA inspects a manufacturing operation (typically referred to as an establishment by the US FDA), they will issue an Establishment Inspection Report (EIR) that describes what the FDA investigator did and details about the establishment's operation. If the investigator observes conditions they deem to be objectionable, these observations (i.e., nonconformities) will be listed on an FDA Form 483 when, in an inspector's judgment, the observed conditions or practices indicate that an FDA-regulated product may be in violation of FDA regulatory requirements. In the best-case scenario in which no objectionable conditions or practices were found or the objectionable conditions found do not justify regulatory action (referred to as No Action Indicated - NAI), it is understood that inspections are just a sampling of the manufacturing operation and that the NAI decision does not reflect FDA's decision making with respect to any potential non-cGMP compliance issues that were not uncovered during the inspection. Thus, the US FDA does not approve or certify a manufacturing operation. Consequently, the best comment that a health product manufacturer whose manufacturing operation has been inspected by the US FDA with NAI can say is that they received no FDA Form 483 observations. Although it is helpful to understand how the US FDA conducts inspections, this process is not the same for all regulatory authorities. For example, the Australian TGA will issue a GMP certification to a manufacturer whose site operations passed a TGA inspection.

* Often the term inspection and audit are used interchangeably. Audits conducted by regulatory authorities are typically described as inspections. An inspection is a tool to detect errors or nonconformance to regulatory requirements, whereas an audit is a systematic, independent, and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which audit criteria are met. The USP DSVP conducts audits to determine compliance or conformity to USP GMP and product quality standards. GMP audits can be a full audit of all 6 GMP quality systems (always for initial audits), or an abbreviated audit of just a few GMP quality systems (sometimes for annual surveillance audits).

4. Information about US Regulations Relevant to USP Standards for Drug Products and Nutritional Supplements

In the US, the drug adulteration and misbranding provisions in section 501(b) and 502(g) of the United States Federal Food, Drug and Cosmetics Act (FDCA) require mandatory compliance with *USP* and *NF* standards. Drug product manufacturers must follow *USP-NF* standards. Although section 403(s) of the FDCA, as amended by the Dietary Supplement Health and Education Act (DSHEA) of 1994, recognizes *USP* and *NF* as the official compendia for dietary supplements, it makes conformance to *USP* and *NF* standards optional unless the dietary supplement is represented as conforming to *USP* or *NF* standards. It is optional for dietary supplement manufacturers to follow *USP-NF* standards except when the manufacturer self affirms on the product label that the product complies with USP standards, or if product is USP verified. Nutritional supplements undergoing verification in the USP DSVP are required to conform to *USP* and *NF* standards. Consequently, KH's UNIMMAP–MMS product, which conforms to the *Expert Consensus UNIMMAP–MMS Product Specification* and has been subjected to the USP DSVP, conforms to USP and NF standards.

5. How Kirk Humanitarian Ensures the Quality of its UNIMMAP-MMS Product

Kirk Humanitarian's UNIMMAP–MMS product is manufactured according to the *Expert Consensus UNIMMAP–MMS Product Specification*. It provides details regarding the quality of ingredients, required stability studies, packaging and labeling, GMP requirements, finished product specification, analytical test methods, and storage and transportation requirements. The *Expert Consensus UNIMMAP–MMS Product Specification* is based primarily on references to USP quality standards critical to ensuring the safety and the purported benefits of a nutritional supplement.

Kirk Humanitarian also requires that its contract manufacturers participate in the USP Dietary Supplement Verification Program (DSVP). The USP DSVP is a comprehensive evaluation and testing program for determining the quality, potency, and purity of dietary supplements. USP dietary supplement verification services include:

- An annual on-site good manufacturing practice (GMP) facility audit for compliance with FDA cGMPs in 21 CFR Part 111 *Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements*, and also with USP's more rigorous GMPs in USP general chapter <2750> *Manufacturing Practices for Dietary Supplements*;
- A thorough review of manufacturing and quality control product documentation that uncovers quality issues that cannot be discovered during a 3–or 5–day GMP facility audit;
- Comprehensive laboratory testing of the finished product for conformance to dietary supplement standards found in the USP–NF;
- Continuous change control monitoring; and
- Off-the-shelf testing of randomly selected samples of products to confirm that USP verified products continue to meet USP's strict standards.

It is primarily the combination of the GMP audit and the product manufacturing and quality control documentation review (which helps ensure compliance to pharmacopeial standards) that helps ensure that the product consistently will be of high quality from batch to batch. This approach is based on the principle that quality needs to be built into the product not tested into the product.

USP awards the USP Verified Mark only after rigorous reviews and testing of product samples, and after the manufacturer has addressed all negative findings (i.e., nonconformities) with appropriate corrective action. Manufacturers must submit for USP's review and approval, all artwork for labels and promotional materials carrying the USP Verified Mark. USP reviews the information to make sure that it contains accurate information about the product and that the Mark is being properly represented. Manufacturers and their verified dietary supplements are posted on the USP website.

Participation in the USP DSVP provides Kirk Humanitarian with the assurance that the products they purchase fully comply with US FDA GMP regulatory requirements and USP GMP and product quality standards. Products that meet the program's rigorous standards are considered "USP Verified" and are awarded use of a distinctive USP Verified Dietary Supplement Mark (or USP Verified Mark) on product labels to demonstrate that the product contains the ingredients listed on the label, in the declared potency and amounts; that it does not contain undesirable levels of specified contaminants, such as, but not limited to heavy metals and microbes; that it will break down and release its contents into the body within a specified amount of time; and that it has been made according to the USP and FDA's current GMPs for dietary supplements, using sanitary and well-controlled procedures.

6. Discussion of UNICEF Technical Requirements

Table 2 provides information regarding various UNICEF technical requirements for nutritional products. UNICEF’s *Technical Requirements Nutritional Products*, item 1 in Table 2, indicates that the technical requirements for a nutritional product depends on the product’s regulatory classification. Where a product is classified as a food or nutritional supplement, UNICEF is guided mainly by the Codex Alimentarius guidelines for specific food ingredients and for vitamin and mineral food supplements (CAC/GL 55 – 2005), Item 5 in Table 2. Vitamin and mineral pharmaceutical products should follow guidance from a relevant pharmacopoeia (Ph. Eur., BP, USP, Ph. Int., etc.) in reference to standards for composition, packaging, and labeling. Item 2 in Table 2 captures the specifications and requirements that apply in general to every product or dosage form. Items 3 and 4 in Table 2 are questionnaires to be completed for each bid (i.e., procurement application), using item 2 as a guide. Items 1 to 4 are related to both pharmaceutical (i.e., drug) and food nutritional supplements, although the documents appear to be directed at pharmaceutical products; Items 5 to 7 are related solely to food nutritional supplement requirements. As shown in Table 2, Kirk Humanitarian (KH) UNIMMAP–MMS products manufactured to the *Expert Consensus UNIMMAP–MMS Product Specification* that are USP verified, comply with the UNICEF technical requirements for both pharmaceutical and food nutritional products.

TABLE 2. Various UNICEF Technical Requirements for Nutritional Products

ITEM #	DOCUMENT NAME	KH UNIMMAP–MMS COMPLIANCE	PRODUCT CLASSIFICATION
1	UNICEF <i>Technical Requirements Nutritional Products</i> (Revision: AMNK, ANS, PSJ; Version: 2.1; Date: 03.05.2017)	Yes	Drug & Food
2	UNICEF (Supply Division) <i>Technical Requirements for Pharmaceutical and Nutrition Products</i> (5th Edition, August 2017), or Finished Product Technical Specifications	Yes ^{1,2}	Drug & Food
3	<i>Interagency finished pharmaceutical product questionnaire</i> (Version 2, July 2014), or Interagency Food or Pharmaceutical Product Questionnaire	Yes ^{2,3}	Drug & Food
4	UNICEF <i>Technical Questionnaire for Pharmaceutical Manufacturers or Interagency Food</i> (Annex 1 – DP 046, Rev 04), or Interagency Food or Pharmaceutical Manufacturers Questionnaire	Yes ²	Drug & Food
5	<i>Codex Guidelines for Vitamin and Mineral Food Supplements</i> (CAC/GL 55 – 2005)	Yes	Food
6	Médecins Sans Frontieres / UNICEF <i>Requirements for stability studies for Therapeutic Foods</i> (Revision: 2, 02/08/2013), or Interagency Requirements for stability studies for Therapeutic Foods	Yes ^{2,4}	Food
7	<i>General Standard for the Labelling of Prepackaged Foods</i> (CODEX STAN 1-1985)	Yes ⁵	Food

TABLE 2 NOTES:

¹ Full testing for each batch is required unless otherwise specified in the Product Technical Specification; UNICEF must approve the manufacturing site; UNICEF must preapprove any changes in formulation, and the manufacturer must provide a copy of product manufacturing license upon request. English and/or French is standard language; other languages may be requested from time to time. Copy of GMP certificate should be submitted, if available. Registration of product in receiving country is necessary if required by the National regulatory authorities.

² The first name listed is the title of the actual document; the second name is how the document is referred to in item 2.

³ Agencies listed on the document include the World Health Organization, The Global Fund, Stop TB Partnership Global Drug Facility, UNFPA, UNICEF, Médecins Sans Frontieres, and Bomite International Geneve (ICRC).

⁴ The interagency document does not list stability conditions for humidity; nevertheless, KH’s product follows ICH Zone IVb stability requirements.

⁵ Different terminology for shelf life is used in the Codex document, e.g., best before date versus expiry date.

7. Conclusion

Kirk Humanitarian's requirement that its contract manufacturers participate in the USP DSVP provides assurance that the products they purchase fully comply with US FDA GMP regulatory requirements, USP GMP and product quality standards, and with UNICEF's technical requirements for nutritional product. Kirk Humanitarian's UNIMMAP-MMS product is made to the same quality standards, whether it would be considered a dietary supplement or a drug product in the United States.



AUTHOR INFORMATION

John B. Atwater, Ph.D.* – Principal Consultant, Ataqua Regulatory Services, Potomac, MD

Phone: +1.301.807.6767 **Email:** jba@ataquars.com

* Formerly, Senior Director of the USP Verification Programs