# INVITATION FOR EXPRESSIONS OF INTEREST (EOI)

The Micronutrient Initiative is an international not-for-profit organization based in Canada, dedicated to eliminating vitamin and mineral deficiencies worldwide.

Every year since 1998, the Micronutrient Initiative (MI) has procured approximately 500 million vitamin A soft gelatin capsules and donated them to UNICEF as In-Kind-Assistance (IKA) for use in national supplementation programs targeting children 6-59 months of age in developing countries.

This year, 2015, MI plans to procure a total of approximately 500 million vitamin A soft gelatin capsules, in 500-and/or 100-count bottles.

The MI therefore invites manufacturers to submit expressions of interest in the supply of vitamin A soft gelatin capsules.

Interested manufacturers must submit an EOI, all prerequisite documents, and product samples, that are to be received on or before **16:00 EST on Wednesday May 6, 2015 ***. Manufacturers are responsible for all costs associated with the EOI preparation.

This expression of interest submission includes all information the MI and UNICEF require to prequalify manufacturers.

Due to stringent quality standards, only prequalified manufacturers will be invited by the MI to bid for the supply of vitamin A soft gelatin capsules in the subsequent Request for Proposals in June 2015. This may involve site visits to confirm Good Manufacturing Practice (GMP).

Manufacturers who are invited to submit proposals to the MI will be asked to quote on supplies to be sent either directly to the UNICEF warehouse in Copenhagen, Denmark (DAP), or to other destinations as specified by the MI.

An MI contract will be issued for the year 2015, and to fulfill an MI contract, the supplies will be required to arrive at the UNICEF warehouse in Copenhagen between October and December, 2015.

* Note: If you have received prequalification status for all or some of your products in the previous year's EOI (EOI reference no. 12-01-0013), you will be receiving a "Provisional Prequalification Extension Letter" issued by the MI and UNICEF, which contains the abbreviated list of required documents to submit with this year's Expression of Interest (12-01-0014).

## (A) PRODUCT DESCRIPTION

### 1. Technical Product Specifications for Vitamin A Soft Gelatin Capsules

### GENERAL

FINISHED PRODUCT

1.1. Vitamin A soft gelatin capsules must be manufactured to comply with the United States Pharmacopeia (USP) Vitamin A Oral Liquid Preparation monograph (USP 37-NF32 or latest edition)[1] or the International Pharmacopoeia (Ph. Int.) Retinol Oral Solution monograph (Ph. Int. Fourth Edition, 3rd Supplement, 2013).

1.2. Halal certification for the Finished Product is required for each batch.

1.3. A vanilla flavouring agent must be added to mask any unpleasant smell or taste.

1.4. Vitamin A soft gelatin capsules must be free of preservatives such as parabens.

1.5. Vitamin A soft gelatin capsules must be suitable for shipment, storage and use world-wide unless otherwise stated. In particular, the vitamin formulation and packaging must be suitable for delivery and use in countries having adverse climatic and storage conditions (e.g. high temperature and humidity, etc. herein considered as Climatic Zones IVa and/or IVb).

1.6. The product shelf life stability must be demonstrated with results of stability studies conducted under long-term testing conditions for climatic Zone IVa and/or Zone IVb countries *****. Proof of shelf life stability is required.

* Compliance to Climatic Zone IVb conditions will be a requirement of the MI/UNICEF Technical Product Specifications for Vitamin A Soft Gelatin Capsules in the 2016 EOI. Earlier compliance is encouraged where possible. Use information provided in WHO TRS No. 953, 2009 - Annex 2 to prepare for compliance.

DESCRIPTION

1.7. Opaque, soft gelatin capsules with nipple to allow for cutting and administration with ease such that the entire vitamin A liquid contents of the capsule can be squeezed gently into the child's mouth.

CAPSULE

Gelatin:

1.8. Gelatin must be without BSE infectivity: Reference is made to the Resolution AP/CSP(99)4, AP/CSP(99)T, to EMEA/410/01 – rev. 1.

1.9. All Gelatin used for the vitamin soft gelatin capsules must be manufactured to meet the criteria described in the latest edition of the International (Ph. Int), United States (USP) or European (Ph.Eur) Pharmacopoeia.

[1] The Dietary Supplements Dosage Forms Subcommittee members have agreed to support the request to reduce the lower limit of vitamin A from NLT 95.0% to NLT 90.0% of labeled claim. This change was reflected in the April, 2013 publication of the USP Revision Bulletin.

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unicef

Hardness:

1.10. The vitamin A soft gelatin capsules procured by MI and UNICEF are used in public health programs worldwide. Unlike other preparations, the soft gelatin capsule is used in this case as a dropper to deliver its liquid contents directly into the recipient's mouth. The capsule is not swallowed. To allow for optimal use of vitamin A soft gelatin capsules in the field, the capsule shell must be hard enough to withstand hot and humid conditions (i.e. not leaking or clumping with other capsules) but soft enough to be used as a dropper such that the entire liquid contents of the capsule can be squeezed gently into the child's mouth with ease by health workers even while dosing numerous children in sequence during campaigns. In addition capsules must not be brittle (i.e. breaking or cracking at the seal when squeezed). In light of these considerations, manufacturers must set their own hardness limits (i.e. minimum and maximum) for (i) stability trials and (ii) point of release as measured by a Bareiss Hardness Tester, or equivalent.

CAPSULE CONTENTS

1.11. The Active Pharmaceutical Ingredient (API) and excipients must comply with the monograph and general notices (and general requirements) from one of the following pharmacopeias: British (BP), European (Ph. Eur.), International (Ph. Int.) or United States (USP).

**Item 1: 200,000 IU VITAMIN A Oral Liquid Preparation (USP)[2] or VITAMIN A Oral Solution (Ph. Int.)[3] as SOFT GELATIN CAPSULES**

Opaque **red**, soft gelatin capsules with nipple.
PMS 187c must be used as a reference pantone colour.
Each soft gelatin capsule must **deliver**:
Vitamin A (Retinol palmitate)…..... 200,000 IU (60 mg) as the API
DL-alpha-tocopherol or tocopheryl acetate …..... 40 IU in oily solution as the antioxidant

Shelf-life: 36-months
500 capsules per bottle

**Item 2: 200,000 IU VITAMIN A Oral Liquid Preparation (USP)[2] or VITAMIN A Oral Solution (Ph. Int.)[3] as SOFT GELATIN CAPSULES**

Opaque **red**, soft gelatin capsules with nipple.
PMS 187c must be used as a reference pantone colour.
Each soft gelatin capsule must **deliver**:
Vitamin A (Retinol palmitate)…..... 200,000 IU (60 mg) as the API
DL-alpha-tocopherol or tocopheryl acetate …..... 40 IU in oily solution as the antioxidant

Shelf-life: 36-months
100 capsules per bottle

[2] USP Vitamin A Oral Liquid Preparation Monograph compliant product.

[3] Ph. Int. Retinol Oral Solution Monograph compliant product.

**Item 3: 100,000 IU VITAMIN A Oral Liquid Preparation (USP)[2] or VITAMIN A Oral Solution (Ph.Int.)[3] as SOFT GELATIN CAPSULES**
Opaque **blue**, soft gelatin capsules with nipple.
PMS 302c must be used as a reference pantone colour.
Each soft gelatin capsule must **deliver**:
Vitamin A (Retinol palmitate)…..... 100,000 IU (30 mg) as the API
DL-alpha-tocopherol or tocopheryl acetate …..... 20 IU in oily solution as the antioxidant

Shelf-life: 36-months
500 capsules per bottle

**Item 4: 100,000 IU VITAMIN A Oral Liquid Preparation (USP)[2] or VITAMIN A Oral Solution (Ph.Int.)[3] as SOFT GELATIN CAPSULES**
Opaque **blue**, soft gelatin capsules with nipple.
PMS 302c must be used as a reference pantone colour.
Each soft gelatin capsule must **deliver**:
Vitamin A (Retinol palmitate)…..... 100,000 IU (30 mg) as the API
DL-alpha-tocopherol or tocopheryl acetate …..... 20 IU in oily solution as the antioxidant

Shelf-life: 36-months
100 capsules per bottle

## 2. Additional Product Information and Quality Standards

**PACKAGING**

2.1. Vitamin A soft gelatin capsules are bottled as 100 or 500 capsules per bottle with a bottle size proportional to its contents. All vitamin A soft gelatin capsules must be kept in tight, light- and tamper-resistant containers. Bottles must conform to the latest edition of British (BP), United States (USP), European (Ph. EUR) or other internationally recognized Pharmacopeia Standard for Pharmaceutical containers and should be suitable for shipment, storage and use worldwide at elevated temperatures and humidity typical of Zone IVa and/or Zone IVb country climate. The bottles must be: tamper-evident opaque plastic securitainer bottles with screw-cap, each containing 100 or 500 capsules and sufficient desiccant material to minimize humidity.

2.2. Vitamin A soft gelatin capsules are packaged in appropriately labeled bottles, including directions for use and delivery of each dosage unit of vitamin A soft gelatin capsules. Statements and Labelling must comply with the relevant pharmacopoeia standard: United States Pharmacopeia (USP) Vitamin A Oral Liquid Preparation monograph (USP 37-NF32 or latest edition) or International Pharmacopoeia (Ph. Int) Retinol Oral Solution monograph (Ph. Int. Fourth Edition, 3rd Supplement, 2013).

## STABILITY

2.3. Vitamin A soft gelatin capsules (Items 1-4) must have a **36-month shelf life** under conditions of high temperature and humidity of Zone IVa and/or IVb. Where the available data on long-term stability of primary batches do not cover the proposed shelf-life at the time of submission, the following minimum requirement is needed to claim three years shelf life:

- Eighteen-month long-term stability data and extrapolation of results to 36-months using stability testing protocols for climatic conditions of high temperature and humidity, Zone IVa and/or IVb from at least three primary batches[4,5]. Note: the extrapolation models used to support shelf life must be in accordance with Q1E Evaluation of Stability Data – Guidance for Industry Section F: General Statistical Approaches (pp. 8-9) and Appendix B (pp. 11-16).
- Six-month accelerated stability data from at least three primary batches[4,5]; and
- A written commitment (signed and dated) to continue long-term testing over the shelf-life period.

2.4. In addition, for products described as Items 1-4 above, shelf life compliance must be demonstrated using a High-performance liquid chromatography (HPLC) assay method to measure vitamin A.

## CERTIFICATION

2.5. The Active Pharmaceutical Ingredients (API) used in the vitamin A soft gelatin capsules must be manufactured and handled according to GMP Standards for Pharmaceutical Products, as certified by an internationally recognized authority that is a member of or partner to the Pharmaceutical Inspection Cooperation Scheme (PIC/S)[6].

2.6. The vitamin A soft gelatin capsules at these high doses of 100,000 IU and 200,000 IU are to be considered pharmaceutical products and must be manufactured in accordance with prevailing Good Manufacturing Practices (GMP) Standards for pharmaceutical products by the National Drug Regulatory Authorities and by an internationally recognized authority that is a member or a partner of the Pharmaceutical Inspection Scheme (PIC/S).

2.7. A certificate of suitability is required to demonstrate that vitamin A, vitamin E and all gelatin used for the vitamin A soft gelatin capsules has been manufactured to meet Pharmacopoeial standards.

2.8. Vitamin A soft gelatin capsules must be certified Halal by an internationally recognized certifying body such as the Islamic Food and Nutrition Council of America (IFANCA) to meet Islamic Halal

[4] Primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing.

[5] Each primary batch should be at minimum pilot scale (one-tenth that of a full production scale batch) and ideally manufactured using different batches of the API.

[6] http://www.picscheme.org/members.php

requirements. This requirement applies to the finished pharmaceutical product and excipient manufacturers involved in the manufacturing process. In the event of prequalification and invitation to submit a proposal, proof of valid certification will be required.

**PRODUCT REGISTRATION**

2.9. Items 1-4, above, should have evidence of registration/marketing authorisation in the country of manufacture/origin. A marketing authorisation from a stringent regulatory authority is desired. Proof of valid registration/market authorization will be required and where this cannot be provided immediately, as an interim measure, manufacturers will be required to submit a Letter of Commitment to obtaining domestic registration status as well as making available any documentation requested by the country of import needed for in-country product registration required to receive the goods.

2.10. Items 1-4, above, should have a Certificate of Pharmaceutical Product (CPP) according to the WHO Certification Scheme, or an equivalent, issued by the National Regulatory Authorities and specified in the WHO Technical Report Series 863.

## (B) PREQUALIFICATION REQUIREMENTS

All manufacturers who wish to participate in the prequalification process must:

1. Submit a cover letter expressing interest in participating, confirming that all information submitted is true and correct, and confirming that their manufacturing facility has the capacity to produce large quantities of the supply (approximately 500 million capsules) in a timely manner for delivery during the months of October through December, 2015.

2. Be capable of manufacturing the product in accordance with the technical specifications and quality standards listed above (see A1 and A2). All vitamin A soft gelatin capsules listed as Items 1-4, above, must be manufactured as a pharmaceutical product.

3. Submit proof of 36-month shelf life of products made in accordance to technical specifications listed above (see A1 and A2). The Minimum Information Requirements for Stability Testing Protocols and Reports are provided in Annex 1 of this document (see pages 10-11).

4. Submit a MI-UNICEF Joint Pharmaceutical Product Questionnaire (PPQ). For a copy of the PPQ, please refer to **Attachment A**. Manufacturers are asked to complete a questionnaire, separately, for each of the product items on offer : 1, 2, 3 and/or 4; for a total of up to four (4) completed questionnaires (see classification system below):

   - **Item 1**: 200,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES, 36-months shelf-life, **500** capsules per bottle;
   - **Item 2:** 200,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES, 36-months shelf-life, **100** capsules per bottle;
   - **Item 3:** 100,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES, 36-months shelf-life, **500** capsules per bottle;
   - **Item 4:** 100,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES, 36-months shelf-life, **100** capsules per bottle.

With these questionnaires, unless otherwise indicated in a "Provisional Prequalification Extension Letter" manufacturers are requested to also submit all supporting documents as specified in the checklist provided on pages 13 and 14 of the Pharmaceutical Product Questionnaire (refer to Attachment A).

**In addition, all <u>new</u> manufacturers, not previously contracted by the MI, must:**

5. Submit a MI-UNICEF Joint Manufacturer Questionnaire (MQ). For a copy of the questionnaire, please refer to **Attachment B**. Contract manufacturers (if any) involved in the manufacturing of products to MI and UNICEF must complete a MQ as well. Manufacturers must also submit all supporting documents as requested in the MQ, such as:

   - A list of all products manufactured by the company and authorized for sale on the domestic market (stating country of origin) and any other products held in other countries;
   - Copy of site master file (PIC-S format).

## (C) SUBMISSION OF EOI

1. All EOI and requisite documentation listed above should be provided in English and refer to EOI reference number: 12-01-0014.

2. **EOI responses, all requisite documentation and samples must be received** at both MI and UNICEF no later than **16:00 EST on Wednesday May 6, 2015** by post, email or fax, at addresses provided below:

   Leeza Sharma
   Micronutrient Initiative
   180 Elgin Street
   Suite 1000
   Ottawa, ON K2P 2K3
   Canada
   Fax: (01) 613-782-6838
   Email: lsharma@micronutrient.org

   Henrik Nielsen
   UNICEF Supply Division
   Oceanvej 10-12
   2150 Nordhavn
   Copenhagen
   Denmark
   Fax:+45 35269421
   Email: hnielsen@unicef.org

3. All enquiries regarding this EOI must be submitted in writing and should be directed to MI using the contact information provided below:

   Leeza Sharma
   Program Officer, Child Survival Commodities
   Micronutrient Initiative
   Fax: (01) 613-782-6838
   Email: lsharma@micronutrient.org

All questions posed and answers provided will be shared by email and posted on the MI website without attribution (see FAQ).

## (D) PREQUALIFICATION EVALUATION

1. All documentation received from manufacturers will be treated as Confidential by the MI and UNICEF.

2. **The MI and UNICEF are not obliged to consider EOIs received after 16:00 EST on Wednesday May 6, 2015.**

3. The pre-qualification evaluation will be conducted by MI and UNICEF. Only those manufacturers who have been successfully prequalified will be **notified by the week of May 25, 2015.**

4. If manufacturers fail to submit sufficient information to complete the prequalification effectively, the MI and UNICEF may terminate the prequalification procedure for that manufacturer's product(s).

5. If manufacturers fail to respond appropriately to subsequent requests for clarification or additional information by the specified date, the MI and UNICEF may terminate the prequalification procedure for that manufacturer's product(s).

6. The MI and UNICEF reserve the right to disqualify any or all manufacturers without incurring any liability to the affected manufacturer(s) or any obligation to inform the manufacturer(s) of the grounds for MI or UNICEF's actions.

## (E) FURTHER REFERENCES:

For background information on the vitamin A supplementation program in infants and children, please refer to the WHO Guideline: Vitamin A supplementation in infants and children 6-59 months of age (Geneva, World Health Organization, 2011).

For information on the USP Vitamin A Oral Liquid Preparation Monograph, please refer to the Vitamin A Oral Liquid Preparation Monograph in USP37-NF32 (or latest edition).

For information on the International Pharmacopoeia Retinol Oral Solution Monograph, please refer to the Retinol oral solution Monograph in Ph. Int. Fourth Edition, 3rd Supplement or latest edition).

For the Certificate of Pharmaceutical Product according to WHO Certification Scheme, please refer to the WHO **Technical Report Series No. 863** Annex 10 entitled Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.(Geneva, World Health Organization, 1996). Please note that an earlier version is not acceptable.

For information on Good Manufacturing Practices (GMP) for pharmaceutical products, please refer to the **WHO Technical Report Series, No. 961** Annex 3 entitled Good Manufacturing Practices for pharmaceutical products: main principles (Geneva, World Health Organization, 2011).

For information on the WHO stability testing guidelines, please refer to the **WHO Technical Report Series, No. 953** Annex 2 entitled Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. (Geneva, World Health Organization, 2009).

For information on evaluation of stability data, please refer to ICH harmonized tripartite Q1E guideline entitled Evaluation for stability data. (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003); and Guidance for Industry - Q1E Evaluation of Stability Data (FDA, June 2004).

For information on quality assurance of pharmaceuticals, please refer to the WHO compendium entitled Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2, 2nd edition - Good manufacturing practices and inspection. (Geneva, World Health Organization, 2007).

For information on Members & Partners to the Pharmaceutical Inspection Co-operation Scheme (PIC/S), please refer to their website: http://www.picscheme.org/members.php.

# Annex 1: Minimum Information Requirements for Stability Testing Protocols and Reports

Table 1. Stability study testing parameters and frequency for vitamin A soft gelatin capsules:
The below table indicates minimum requirements

| Storage | | Testing parameters | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | General appearance | | Assay of capsule contents/fill | | | Functionality | Level of microbial contamination[7] |
| Testing interval | Condition | Vit. A oil[8 or 9] | Soft gel caps[10] | Vit.A[11 or 12] | Vit. E | Uniformity of dosage units | Hardness | |
| Specifications | | Pass/ fail | Pass/ fail | 90.0-120.0% of labeled amount of Vit. A | Limits (min. and max. as % LC) of Vit. E | Meets USP <905> requirement or Meets Ph. Int. Uniformity of deliverable dose (single-dose container) requirement | Limits (min. and max. in Newtons) to be provided by mfrs | Total viable count (NMT$10^4$/g) Yeast- mold (NMT $10^2$/g) Entero bac. (NMT $10^2$/g) Absence of E.Coli, Staph.aureus, Salmonella |
| | | | | *Report in IU and %* | | | | |
| Initial* | | X | X | X | X | X | X | X |
| **Accelerated** | | | | | | | | |
| 1 Month | 40ºC ± 2ºC/75% RH ± 5% RH | X | X | X | X | X | X | X |
| 2 Months | | X | X | X | X | X | X | X |
| 3 Months | | X | X | X | X | X | X | X |
| 6 Months | | X | X | X | X | X | X | X |
| **Long-term** | | | | | | | | |
| 3 Months | 30ºC ± 2ºC/65% or 75% RH ± 5% RH | Δ | Δ | Δ | Δ | Δ | Δ | |
| 6 Months | | Δ | Δ | Δ | Δ | Δ | Δ | |
| 9 Months | | Δ | Δ | Δ | Δ | Δ | Δ | |
| 12 Months | | Δ | Δ | Δ | Δ | Δ | Δ | |
| 18 Months | | Δ | Δ | Δ | Δ | Δ | Δ | Δ |
| 24 Months | | Δ | Δ | Δ | Δ | Δ | Δ | |
| 36 Months | | Δ | Δ | Δ | Δ | Δ | Δ | Δ |

*Time point "0" (TP0), the initial time point, should correspond to the study start date, i.e. the day the product is placed in the appropriate stability chamber. Subsequent time points indicate the time at which the samples are removed from the stability chamber in reference to TP0 as described above.

[7] Ph. Eur 6th Total viable count 2.6.12/2.6.13 Tests for specified microorganisms (Pharmaceuticals products which contain excipients/APIs of animal origin).
[8] Current official version of USP – VA OLP monograph (Identification)
[9] Current official version of Int. Ph. – Retinol Oral Solution monograph (Identity test)
[10] To be defined by mfrs to meet MI/UNICEF technical specification – Look for organoleptic properties such as leaking, clumping, melting, etc.
[11] USP – VA OLP monograph (Assay Vit A). As per official correspondence with the USP, the Dietary Supplements Dosage Forms Subcommittee members have agreed to support the request to reduce the lower limit of vitamin A from NLT 95.0% to NLT 90.0% of labeled claim. This change was reflected in the April, 2013 publication of the USP Revision Bulletin.
[12] Current official version of Int. Ph. – Retinol Oral Solution monograph (Assay).

**Evaluation of data required**

A systematic approach should be adopted for the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form *(for example, hardness for softgel capsules where an oral solution is the dosage form)*. Stability studies should be presented in an appropriate format (e.g. tabular, graphical and narrative).
In addition to *Table 1,* above, the stability study reports need also to include:

- FPP: Ingredients & formulation, dosage strength, batch number, size and mfg date;
- API: Ingredients & formulation, manufacturer and batch number;
- Packaging: Description, materials used, and no. of units per container;
- Study start date, individual time points and total duration of the study;
- Specification / Acceptability limits for each parameter tested;
- For quantitative tests, actual numerical results should be provided (avoid using terms like "within limits" or "conforms");
- Information on analytical procedures used to generate the data and validation of these procedures (if applicable);
- Information on characterization of impurities;
- Extrapolation to proposed shelf life (i.e. 36 months) where long-term stability data do not cover the proposed shelf-life. Note: the extrapolation models used to support shelf life must be in accordance with Q1E Evaluation of Stability Data – Guidance for Industry Section F: General Statistical Approaches (pp.8-9) and Appendix B (pp. 11-16)[13]*;*
- Study conclusions.

Any variation introduced to the FPP such as changes in the formulation, manufacturing process, container closure system, properties of the packaging materials etc. that could adversely affect the stability of the product and/or where the existing data no longer supports the quality, safety or efficacy of the varied product throughout its shelf life must be reported to MI and UNICEF for assessment.

[13] Source: Guidance for Industry – Q1E Evaluation of Stability Data (FDA, June 2004).