ANNEX B: Product Technical Specifications

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

Item No.	Product Type	Description
Item 1	**200,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES** **500 capsules per bottle** **Desired Shelf-life: 36 months**	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
Item 2	**200,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES** **100 capsules per bottle** **Desired Shelf-life: 36 months**	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
Item 3	**100,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph.Int.) as SOFT GELATIN CAPSULES** **500 capsules per bottle** **Desired Shelf-life: 36-months**	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
Item 4	**Item 4: 100,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph.Int.) as SOFT GELATIN CAPSULES** **100 capsules per bottle** **Desired Shelf-life: 36-months**	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

GENERAL PRODUCT TYPE & DESCRIPTION

FINISHED PRODUCT

1.1. Vitamin A soft gelatin capsules must be manufactured to comply with the United States Pharmacopeia (USP[1]) Vitamin A Oral Liquid Preparation monograph (USP 37-NF32 or latest edition)[2] or the International Pharmacopoeia (Ph. Int.[3]) 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. Vitamin A of Non-Bovine origin preferred.

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

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

1.6. Vitamin A soft gelatin capsules must be suitable for shipment, storage and use world-wide. 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 IVb).

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

DESCRIPTION

1.8. 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:

1.9. 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.

1.10. 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.

Hardness:

1.11. The vitamin A soft gelatin capsules procured by NI 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

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

[2] 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.

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

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

1.12. 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).

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 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).

2.3. The secondary packaging for vitamin A soft gelatin capsules must comply with the current UNICEF Warehouse Packing Technical Standards and Specifications.[4]

STABILITY

2.4. Vitamin A soft gelatin capsules (**Items 1-4) should** demonstrate 36 months of shelf life under conditions of high temperature and humidity of Zone IVb. However, NI/UNICEF may consider conditionally prequalifying manufacturers with products having at minimum 12 months Zone IVb stability data and 6 months of accelerated stability data with regular follow up to track progress and technical support provided by both NI and UNICEF. With submission of the following strictly required.

2.5. Preference will be given to products that demonstrate a longer shelf life. Submission of the following will be required:

- Stability data from at least three primary batches[5,6], and
- A written commitment (signed and dated) to continue long-term testing over the shelf-life period.

2.6. 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.

[4]UNICEF Warehouse Packing Specifications:
https://www.unicef.org/supply/files/CPH_WH_only_packing_specifications_April_2017.pdf

[5] 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.

[6] 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

2.7. In addition, in- use stability data, if available can also be submitted. For this RFP, in-use stability testing data is not a mandatory requirement.

CERTIFICATION

2.8. 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)[7].

2.9. 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).

2.10. A certificate of suitability (CEP) 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.

2.11. 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 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.

2.12. In addition, GMO free and Radiation free certificates, if available for the manufacturing sites can also be submitted. For this RFP, GMO and Radiation free certificates are not a mandatory requirement.

PRODUCT REGISTRATION

2.13. **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. The manufacturer bears responsibility for all associated costs related to product registration/marketing authorization.

2.14. **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.

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

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[8]
Testing interval	Condition	Vit. A oil[9 or 10]	Soft gel caps[11]	Vit.A[12 or 13]	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 (NMT10^4/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.

[8] 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).
[9] Current official version of USP – VA OLP monograph (Identification)
[10] Current official version of Int. Ph. – Retinol Oral Solution monograph (Identity test)
[11] To be defined by mfrs to meet NI/UNICEF technical specification – Look for organoleptic properties such as leaking, clumping, melting, etc.
[12] 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.
[13] 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 reference / 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;
- 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 NI and UNICEF for assessment.