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[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. 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.
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 IV b conditions will be a requirement of the MI/UNICEF Technical Product Specifications for Vitamin A Soft Gelatin Capsules in the 2019 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.

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

[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.

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 No.	Product Type	Description
Item 10	**S1583000 Retinol 200,000IU soft gel.caps/PAC-500** **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 20	**S1583015 Retinol 100,000IU soft gel.caps/PAC-500** **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 30	**S1583010 Retinol 200,000IU soft gel.caps/PAC-100** **200,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES** **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 40	**S1583020 Retinol 100,000IU soft gel.caps/PAC-100** **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

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).

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 IVa and/or IVb. However, products with at least 24 months of shelf life would be acceptable. 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

2.5. 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.

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