TECHNICAL NOTE
QUALITY AND REGULATORY CONSIDERATIONS FOR THE USE OF VITAMIN A SUPPLEMENTS IN PUBLIC HEALTH PROGRAMMES FOR INFANTS AND CHILDREN AGED 6–59 MONTHS
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QUALITY AND REGULATORY CONSIDERATIONS FOR THE USE OF VITAMIN A SUPPLEMENTS IN PUBLIC HEALTH PROGRAMMES FOR INFANTS AND CHILDREN AGED 6–59 MONTHS

World Health Organization
Technical note: quality and regulatory considerations for the use of vitamin A supplements in public health programmes for infants and children aged 6–59 months


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# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABBREVIATIONS</td>
<td>IV</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>V</td>
</tr>
<tr>
<td>Financial support</td>
<td>V</td>
</tr>
<tr>
<td>SCOPE AND PURPOSE</td>
<td>1</td>
</tr>
<tr>
<td>VITAMIN A</td>
<td>1</td>
</tr>
<tr>
<td>Functions and dietary sources</td>
<td>1</td>
</tr>
<tr>
<td>Public health relevance</td>
<td>2</td>
</tr>
<tr>
<td>VITAMIN A SUPPLEMENTATION</td>
<td>2</td>
</tr>
<tr>
<td>From a few deficiency surveys to a global programme</td>
<td>2</td>
</tr>
<tr>
<td>Efficacy of vitamin A supplements in infants and children aged 6–59 months</td>
<td>3</td>
</tr>
<tr>
<td>Safety evidence</td>
<td>5</td>
</tr>
<tr>
<td>WHO guidelines and recommendations on vitamin A supplementation in infants and children aged 6–59 months</td>
<td>7</td>
</tr>
<tr>
<td>QUALITY-RELATED REGULATORY STANDARDS FOR VITAMIN A AS A MEDICAL PRODUCT</td>
<td>9</td>
</tr>
<tr>
<td>WHO medicines quality assurance guidelines</td>
<td>10</td>
</tr>
<tr>
<td>Vitamin A finished product specifications</td>
<td>15</td>
</tr>
<tr>
<td>CLOSING REMARKS AND KNOWLEDGE GAPS</td>
<td>22</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>23</td>
</tr>
<tr>
<td>ANNEX 1 THE INTERNATIONAL PHARMACOPOEIA RETINOL ORAL SOLUTION MONOGRAPH</td>
<td>30</td>
</tr>
<tr>
<td>ANNEX 2 UNITED STATES PHARMACOPEIA VITAMIN A ORAL LIQUID PREPARATION MONOGRAPH</td>
<td>32</td>
</tr>
<tr>
<td>ANNEX 3 NUTRITION INTERNATIONAL/UNITED NATIONS CHILDREN’S FUND PRODUCT TECHNICAL SPECIFICATIONS</td>
<td>34</td>
</tr>
</tbody>
</table>
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DEVTA trial</td>
<td>Deworming and Enhanced Vitamin A trial</td>
</tr>
<tr>
<td>DTP</td>
<td>diphtheria, tetanus and pertussis</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agriculture Organization of the United Nations</td>
</tr>
<tr>
<td>GMP</td>
<td>good manufacturing practices</td>
</tr>
<tr>
<td>ICSR</td>
<td>individual case safety report</td>
</tr>
<tr>
<td>IU</td>
<td>international unit</td>
</tr>
<tr>
<td>IVACG</td>
<td>International Vitamin A Consultative Group</td>
</tr>
<tr>
<td>MCV</td>
<td>measles-containing vaccine</td>
</tr>
<tr>
<td>RE</td>
<td>retinol equivalent</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children's Fund</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
This technical note was coordinated by the World Health Organization (WHO) Department of Nutrition and Food Safety. Mr Filiberto Beltran-Velazquez, with technical support from Dr Maria Nieves Garcia-Casal, Dr Juan Pablo Peña-Rosas and Dr Lisa Rogers, oversaw the preparation of this document. WHO gratefully acknowledges the technical input of Andrea Monahan and Leeza Sharma from Nutrition International, as well as technical staff from UNICEF Supply Division.

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SCOPE AND PURPOSE

Vitamin A supplementation programmes for infants and young children aged 6–59 months have been implemented since the mid-1990s for the reduction of morbidity and mortality in low- and middle-income countries where vitamin A deficiency is a known or suspected public health problem. The World Health Organization (WHO) received requests from Member States, nongovernmental agencies and other intergovernmental organizations for a technical note regarding vitamin A capsules for use in vitamin A supplementation programmes, in order to summarize (i) the quality and regulatory considerations to take into account when producing and distributing vitamin A capsules for infants and young children aged 6–59 months; and (ii) the available evidence on the efficacy and safety of vitamin A supplementation.

This document is intended for national regulators; senior technical and programme staff in government regulatory agencies and other organizations involved in vitamin A supplementation programmes; and people involved in the manufacture, procurement, importation or distribution of vitamin A capsules in countries. It is not intended for field staff involved in the management of vitamin A deficiency.

VITAMIN A

Functions and dietary sources

Vitamin A is an essential fat-soluble vitamin required for normal visual function, epithelial cellular integrity, immune function, growth, development and reproduction. Different forms of vitamin A, such as retinol, retinyl esters, retinal and retinoic acid, serve different functions in the body (1).

Two forms of vitamin A can be found in the diet: preformed vitamin A and provitamin A carotenoids. Preformed vitamin A is found in animal products such as milk, fish, meats (particularly liver), egg yolk, dairy products, fortified foods and supplements. Provitamin A carotenoids, primarily beta-carotene, alpha-carotene and beta-cryptoxanthin, are found predominantly in green leafy vegetables and yellow or orange fruits and vegetables (2, 3).

WHO and the Food and Agriculture Organization of the United Nations (FAO) estimate that the mean daily requirement of this nutrient ranges between 180 μg and 200 μg retinol equivalents (RE)/day (see Table 1) in infants and children (3).

Table 1. Estimated mean requirements for vitamin A intake in infants and children (3)

<table>
<thead>
<tr>
<th>Age</th>
<th>Estimated mean requirement (µg RE/day)</th>
<th>(IU* day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 months</td>
<td>180</td>
<td>600</td>
</tr>
<tr>
<td>7–11 months</td>
<td>190</td>
<td>633</td>
</tr>
<tr>
<td>1–3 years</td>
<td>200</td>
<td>667</td>
</tr>
<tr>
<td>4–6 years</td>
<td>200</td>
<td>667</td>
</tr>
</tbody>
</table>

IU: international units; RE: retinol equivalents.

*1 RE retinol = 1 μg or 0.3 IU retinol; 1 IU retinol = 0.3 μg retinol or 0.33 RE.

The absorption efficiency of preformed vitamin A, as the form found in supplements, is typically higher than 70% and may remain at the same level with further increases of ingested preformed vitamin A. Absorption and conversion of provitamin A are more limited, owing to negative feedback mechanisms (2). The liver is the primary storage site of vitamin A, with most stored in stellate cells as retinyl ester (4).
Vitamin A deficiency causes several clinical symptoms, including xerophthalmia, night blindness, Bitot spots, keratomalacia, corneal scars and permanent blindness. Another major consequence of deficiency is increased risk of several health problems, such as respiratory diseases, diarrhoea, measles and vision complications (5, 6).

Infections and vitamin A deficiency often overlap and negatively exacerbate each other. Infections deplete vitamin A status, by reducing appetite and nutrient absorption while increasing metabolism and excretion (7). Together, these form a cycle of increased vitamin A deficiency, morbidity and mortality (5).

Public health relevance
Vitamin A deficiency is of significant public health concern, particularly in lower-income countries. Globally, 5.17 million preschool children have night blindness and 190 million have low serum retinol; these represent 0.9% and 33.3%, respectively, of children in countries considered to be at risk of vitamin A deficiency (5).

A more recent analysis of trends in vitamin A deficiency in preschool children in low- and middle-income countries between 1991 and 2013 demonstrated a decrease in its overall prevalence from 39% to 29%. This global decrease was driven primarily by reductions in east and south-east Asia, Oceania, Latin America and the Caribbean. The prevalence in south Asia and sub-Saharan Africa remains high at 47% and 45%, respectively (6).

This deficiency has a direct effect on child mortality. It is estimated that 94,500 diarrhoea- and 11,200 measles-related deaths per year are attributable to vitamin A deficiency, with most of these deaths occurring in sub-Saharan countries and south Asia. Together, these represent 1.7% of all child deaths in low- and middle-income countries (6).

From these data, it is evident that a comprehensive approach is needed to improve vitamin A status in these regions. It may include dietary diversification, increased access to vitamin-rich foods, vitamin A supplementation and improved access to health facilities in order to treat infectious diseases (6).

VITAMIN A SUPPLEMENTATION
From a few deficiency surveys to a global programme
The story of vitamin A supplementation begins in 1962, when a global survey commissioned by WHO revealed that xerophthalmia was widely spread in Asia, Africa and Latin America (8). To better understand and address this global problem, the International Vitamin A Consultative Group (IVACG) was formed in 1975, with south-east Asia as priority (9).

In the following years, studies in Indonesia reported a positive association between vitamin A deficiency and mortality rates in preschool children. Children with mild xerophthalmia had mortality rates approximately four times higher than children without xerophthalmia (10). Further, 16% of all deaths in children aged 1–6 years were attributable to mild vitamin A deficiency (11). These observations made clear that vitamin A deficiency needed a straightforward solution and became the basis of a series of randomized controlled trials in which children received vitamin A supplementation.

In the early 1990s, a series of meta-analyses on subsets of 10 mortality trials reported that vitamin A supplementation decreased child mortality by 23–34% (12–15). As a result, this intervention received increased recognition and consensus since 1992 (16), although it is acknowledged that the effectiveness and magnitude of supplementation probably depend on the population (17, 18).

for the use of vitamin A supplementation in the treatment and prevention of vitamin A deficiency and xerophthalmia, which recommended vitamin A supplementation in children younger than 6–59 months (21).

In 2011, WHO published the current guidelines for vitamin A supplementation in different target groups in settings where vitamin A deficiency is a public health problem. Supplementation is recommended for children aged 6–59 months, for the reduction of morbidity and mortality in accordance with previous recommendations (17).

Currently, vitamin A supplementation is distributed globally and provided in 82 countries (22). The proportion of children aged 6–59 months who received vitamin A supplementation between 2004 and 2014 by WHO region was as follows: Africa, 59%; Americas, 36%; Eastern Mediterranean, 46%; Western Pacific, 84%; global, 59% (23). Globally, full vitamin A supplementation coverage for high-priority countries was 64% in 2016 (24).

**Efficacy of vitamin A supplements in infants and children aged 6–59 months**

Based on multiple randomized trials and meta-analyses, vitamin A supplementation has the effects discussed under the subheadings that follow.

*Vitamin A supplementation reduces overall risk of death and diarrhoea-related mortality in children aged 6–59 months who are deficient in vitamin A*

In 2010, a Cochrane systematic review and meta-analysis included 43 studies that followed approximately 200,000 children aged 6–59 months who were administered vitamin A supplementation using the WHO recommendation doses of 100,000 international units (IU) for children aged 6–11 months and 200,000 IU for children aged 12 months to 59 months (17). A meta-analysis of 17 trials for all-cause mortality indicated that vitamin A reduces the overall risk of death by 24% (relative risk [RR] 0.76, 95% confidence interval [CI] 0.69–0.83) (25).

In 2013, the Deworming and Enhanced Vitamin A (DEVTA) trial (26) was published, contradicting the findings of previous studies by reporting that vitamin A supplementation may have only a modest effect on child mortality. The DEVTA trial was conducted with approximately 1 million children in northern India and demonstrated no effect of vitamin A supplementation on all-cause mortality (RR 0.96, 95% CI 0.89–1.03). Further, there were no differences between groups among causes of death, including diarrhea, pneumonia, measles, malnutrition or other causes (26). Several researchers identified multiple design limitations of the DEVTA trial and cited criticisms of the trial’s methods and conclusions (27).

In 2017, an updated Cochrane systematic review was conducted, adding four additional studies, including the DEVTA trial, for a total of 47 studies comprising approximately 1.2 million participants (28). Studies were geographically diverse across 19 countries: 30 were conducted in Asia, 16 in India, 8 in Africa, 7 in Latin America and 2 in Australia. Most included equal numbers of boys and girls. Participants were administered vitamin A supplementation every 4–6 months with 100,000–200,000 IU, depending on the age of participants, by WHO recommendation (17). Five of the 47 studies used smaller but more frequent doses of vitamin A. Data on the effect of vitamin A supplementation for the prevention of death were available from 19 of the included studies; the combined results indicated that vitamin A reduces the overall risk of death and diarrhea-related death by 12% (RR 0.88, 95% CI 0.83–0.93) (28).

With the addition of the DEVTA trial (weight of 61.7% in the meta-analysis), a 12% reduction of all-cause mortality risk was observed (RR 0.88, 95% CI 0.83–0.93), a decrease from the previous estimate of 24%. The review reported that vitamin A supplementation was effective in reducing diarrhea-related mortality (RR 0.88, 95% CI 0.79–0.98), but was not significant for measles, malaria, meningitis or lower respiratory tract infections. In addition, vitamin A supplementation significantly reduced the incidence of diarrhea (RR 0.85, 95% CI 0.82–0.87) and measles (RR 0.50, 95% CI 0.37–0.67) (28).
**Vitamin A supplementation prevents sequelae of vitamin A deficiency such as night blindness, Bitot spots and xerophthalmia, in geographical areas where vitamin A deficiency is prevalent**

In high-risk populations, frequent vitamin A supplementation is known as one of the most important intervention strategies to improve vitamin A status and prevent nutritional blindness. Frequent administration of vitamin A provides protection against developing mild xerophthalmia, for 4–6 months. The efficacy of vitamin A supplementation in the prevention of mild xerophthalmia is strongly associated with supplementation coverage. In children aged 1–4 years, 65–85% coverage of vitamin A supplementation yielded a reduction in the prevalence of vitamin A deficiency by 80–90% (29).

Administration of 50 000–200 000 IU of vitamin A every 4–6 months to children aged 2 months to 5 years eliminated night blindness entirely and prevented new incidence of Bitot spots in a significant number of children (30). Frequent vitamin A supplementation reduced the incidence of keratomalacia by about 80% when compared with the area not covered by vitamin A supplementation programming (31). The ability of vitamin A supplementation to protect against xerophthalmia is affected by the seasonal patterns of xerophthalmia and other factors affecting vitamin A status. High-dose vitamin A supplementation provided to children in Nepal significantly reduced the prevalence (63% reduction) and incidence (62% reduction) of xerophthalmia (32).

Clinical signs of vitamin A deficiency, such as active xerophthalmia, are unusual findings among infants, because vitamin A is obtained from breast milk (33). Neonates are born with approximately 6 μmol of stored vitamin A, which increases to 70 μmol within 6 months, as long as the infant is exclusively breastfed by a well-nourished mother. In some low- and middle-income countries, however, breast milk contains half the vitamin A concentration of breast milk in high-income nations. While infants in some low- and middle-income countries are born with the same vitamin A stores, within the first 6 months of life consumption from breast milk is only sufficient to meet basal vitamin A requirements; they have almost no capability for storage. If introduced complementary foods are also low in vitamin A, these children are at high risk for developing vitamin A deficiency (34). In studies in Bangladesh, Brazil and Indonesia, investigators observed that 25–90% of infants aged 6 months had insufficient liver storage of vitamin A (33). Many infants from low- and middle-income countries will remain deficient and require vitamin A from external sources, despite having been breastfed. The goal of vitamin A supplementation is to amplify the liver storage of vitamin A with minimal risk of toxicity. The amount of each dose is aimed to prevent clinically noticeable ocular disease, particularly during high-risk circumstances such as infection or depleted dietary intake of vitamin A (33).

In a study in Indonesia, vitamin A supplementation was administered to a population with a 4.7% prevalence of xerophthalmia. Results indicated a significant difference between the resulting prevalence of xerophthalmia in children who received vitamin A supplementation (0.5%, \( P < 0.001 \)) and those who received placebo (3.6%, \( P < 0.001 \)). At 6 months, administration of a single dose of 200 000 IU of vitamin A effectively reduced xerophthalmic lesions among 91% of participants (35).

In a meta-analysis published in 2017 (28), the studies that assessed the effects of vitamin A supplementation for children aged 6–59 months on the prevalence (32, 36) and incidence (32, 37, 38) of xerophthalmia administered vitamin A supplementation at dosages aligned with current WHO recommendations (100 000 IU for children aged 6–11 months, 200 000 IU for children aged 12–59 months (17)). One of the studies (32) included in the meta-analysis showed that the administration of 200 000 IU of vitamin A supplementation every 4 months to children aged 1–4 years for 16 months reduced the prevalence (RR 0.37, 95% CI 0.17–0.79) and apparent incidence (RR 0.38, 95% CI 0.14–1.00) of xerophthalmia. According to this study, children who received vitamin A supplementation are less likely to experience both incidence and persistence of Bitot spots (32).

This above-mentioned Cochrane systematic review and meta-analysis of vitamin A supplementation in children also summarized the incidence and prevalence of Bitot spots, night blindness and xerophthalmia at longest follow-up (28). Five studies demonstrated a significant reduction in the prevalence of Bitot spots at longest follow-up (RR 0.42, 95% CI 0.33–0.53). One study reported no significant effect on the incidence of Bitot spots (RR 0.93, 95% CI 0.76–1.14). One study reported a significant reduction in the incidence of night
blinding (RR 0.53, 95% CI 0.28–0.99). Two studies reported a significant reduction in the prevalence of night blindness (RR 0.32, 95% CI 0.21–0.50). Three trials did not demonstrate a combined effect on the incidence of xerophthalmia at longest follow-up (RR 0.85, 95% CI 0.70–1.03), but there was a significant reduction in the prevalence of xerophthalmia at longest follow-up in two studies (RR 0.31, 95% CI 0.22–0.45).

**Safety evidence**

*Potential adverse events associated with high-dose vitamin A supplementation in target populations*

The recommended safe daily intake for children aged 1–3 years is 400 µg, equal to 1333 IU (see Table 2). The amount and frequency of vitamin A supplementation that can be given without causing toxicity are dependent on absorption, storage and utilization (39).

**Table 2. Estimated safe levels of vitamin A intake in infants and children**

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended safe intake (µg RE/day)</th>
<th>(IUa/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 months</td>
<td>375</td>
<td>1250</td>
</tr>
<tr>
<td>7–11 months</td>
<td>400</td>
<td>1333</td>
</tr>
<tr>
<td>1–3 years</td>
<td>400</td>
<td>1333</td>
</tr>
<tr>
<td>4–6 years</td>
<td>450</td>
<td>1500</td>
</tr>
</tbody>
</table>

IU: international units; RE: retinol equivalents.

Several studies have found evidence of adverse effects with vitamin A supplementation of 300 000 IU or higher in children aged 6–59 months (39). Factors associated with side-effects from vitamin A supplementation include giving too high a dose, using the aqueous form, and lack of vitamin E. The current recommendations are for vitamin A supplementation given orally in oily form with added vitamin E, and with doses of 100 000 IU for children aged 6–11 months and 200 000 IU for children aged 12–59 months (17).

The side-effects of the currently recommended doses for vitamin A supplementation are generally considered uncommon and transient in children aged 6 months or older (28). In the 2017 meta-analysis (28), vomiting within 48 hours was identified as the primary side-effect of vitamin A supplementation relative to control in this age group; no significant difference in bulging fontanelle was identified. Absolute rates of vomiting in vitamin A supplementation and control groups were, respectively, 3.9% and 0% (30), 8.8% and 2.2% (includes nausea or vomiting) (40), 10.3% and 8.2% (41), and 5% and 4% (42). Vomiting resolved after the first day and did not happen with subsequent doses (30). Most symptoms appear within 24 hours following vitamin A supplementation and resolve without treatment within 12–24 hours (40).

The toxicity reaction is thought to occur if the levels of serum retinol and retinoic acid and other retinoids are high enough to trigger the reaction. In general, single administration of vitamin A with doses greater than 300 000 IU in children may cause acute hypervitaminosis A (39). Acute toxicity in infants and children is characterized by nausea, vomiting, headache, anorexia, drowsiness, irritability, increase in cerebrospinal fluid and intracranial pressure, vertigo, blurred vision, muscular incoordination and bulging fontanelle (43, 44). Symptoms of acute toxicity are usually temporary and abate soon after cessation of vitamin A administration (39).

Chronic toxicity is caused by a high intake of vitamin A (preformed vitamin A), with doses of 2500–50 000 IU per kilogram of body weight per day for days to years (3, 43). Both acute and chronic toxicity are associated with increased concentration of plasma retinyl esters and show higher sensitivity in infants. Forms of vitamin A also determine the toxicity: vitamin A in an aqueous form is more likely to produce toxicity than vitamin A in oil (39).
Symptoms of chronic hypervitaminosis are nonspecific and may involve chronic nervous system symptoms, liver abnormalities, or bone and skin symptoms. In infants and children, chronic hypervitaminosis may cause anorexia and skin problems such as dryness, itch or rash. Other possible manifestations include alopecia, bristly hair, increasing intracranial pressure, angular fissures of the lips, irritability, and tenderness and swelling of the extremities. In addition, chronic hypervitaminosis may cause hyperostosis, hepatomegaly and growth failure (39, 43). Prominent chronic adverse effects of vitamin A intake include reduced bone mineral density and liver abnormalities (2).

A group of experts described 65 instances of children being identified as having chronic and sub chronic low-dose vitamin A toxicity, as determined through reported excessively high intake of vitamin A for the majority of the child’s life (39). Of these cases, 46 were in infants aged 6–59 months. The daily doses of vitamin A to which infants had been exposed ranged from 12 000 IU to 600 000 IU, with durations ranging from 7 days to 3 years. An observed 26% of infants aged 6–59 months were recorded to have received treatment that included vitamin D – the effects of excessive intake of vitamin D are difficult to differentiate from chronic hypervitaminosis A. Children and infants were observed to have high tolerance to high-dose vitamin A supplementation; after administration of 2500–50 000 IU/kg, a number of children experienced the disappearance of chronic toxicity symptoms within months to a year after cessation of administration. The time needed to recover was dependent upon the dose and duration of administration. The experts also reported 125 cases of acute hypervitaminosis in infants and children who mainly received an aqueous form of vitamin A at doses ranging from 300 000 IU to 900 000 IU (39). Selected publications contributing to current knowledge on the side-effects of vitamin A supplementation in children are presented in Table 3.

Table 3. Selected publications contributing to current knowledge of side-effects of vitamin A supplementation in children

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of children</th>
<th>Age</th>
<th>Dosage form</th>
<th>Dose (IU)</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy, 1969 (45)</td>
<td>100</td>
<td>0.5–5 years</td>
<td>Aqueous</td>
<td>300 000</td>
<td>25% side-effect symptoms</td>
</tr>
<tr>
<td>Swaminathan et al., 1970 (46)</td>
<td>1785</td>
<td>1–5 years</td>
<td>Oily</td>
<td>300 000</td>
<td>4% side-effect symptoms</td>
</tr>
<tr>
<td>Sinha and Bang, 1976 (30)</td>
<td>153</td>
<td>2–6 years</td>
<td>Oily</td>
<td>200 000</td>
<td>6 of 153 vomited after first dose</td>
</tr>
<tr>
<td>Reddy, 1978 (47)</td>
<td>10–20 million</td>
<td>1–4 years</td>
<td>Oily</td>
<td>200 000</td>
<td>1–4% acute hypervitaminosis, e.g. vomiting, malaise</td>
</tr>
<tr>
<td>Solon et al., 1979 (48)</td>
<td>About 500</td>
<td>1–16 years</td>
<td>Oily</td>
<td>200 000</td>
<td>3.4% vomiting, headaches and fever</td>
</tr>
<tr>
<td>Florentino et al., 1990 (40)</td>
<td>2471</td>
<td>1–6 years</td>
<td>Oily</td>
<td>100 000 or 200 000</td>
<td>200 000 IU group: 8.8% nausea and vomiting, 5.9% headache, 6% diarrhoea, 7.9% fever</td>
</tr>
<tr>
<td>Arya et al., 2000 (41)</td>
<td>256</td>
<td>9–12 months</td>
<td>Oily</td>
<td>100 000</td>
<td>12.1% vomiting, 19.6% irritability; neither significantly different from control group</td>
</tr>
<tr>
<td>Fisker et al., 2013 (42)</td>
<td>1673</td>
<td>6–17 months</td>
<td>Oily</td>
<td>100 000 (aged &lt;1 year), 200 000 (aged ≥1 year)</td>
<td>Overall clinical symptoms (bulging fontanelle, vomiting, convulsion, irritability)</td>
</tr>
<tr>
<td>Imdad et al., 2017 (28)</td>
<td>10 541</td>
<td>6–59 months</td>
<td>Oily</td>
<td>Meta-analysis</td>
<td>Significant increase in vomiting compared with placebo (RR 1.97, 95% CI 1.44–2.69)</td>
</tr>
</tbody>
</table>

CI: confidence interval; RR: relative risk.
*Adapted from Bauernfeind, 1980 (39) and Imdad et al., 2017 (28); all doses given as retinyl palmitate.
An analysis of the WHO global database for individual case safety reports (ICSRs) VigiBase (49) identified 205 ICSRs of suspected adverse medicine reactions reported in children aged 0–5 years who had used vitamin A. Extracted reports included ICSRs received from 1968 to January 2018. The ICSRs in this age group originated from 24 different countries, mainly from Zimbabwe (133 reports, 65%) and India (14 reports, 7%). The main suspected adverse reactions reported were vomiting (100 ICSRs), diarrhoea (83 ICSRs), pyrexia (36 ICSRs) and rash (20 ICSRs).

A total of 82% of ICSRs (168/205) in this age group reported an adverse medicine reaction as serious; however, only 46 of these 168 serious ICSRs specified the serious criteria: 31 ICSRs caused or prolonged hospitalization, another 6 were life-threatening, and another 8 resulted in death; vitamin A supplementation was assessed as possible in three and probable in one of these deaths during a causality assessment.2

Potential interaction between vitamin A supplementation and vaccination

Vitamin A supplementation should be delivered once to infants aged 6–11 months and then twice a year to children aged 12–59 months, during health-system contacts, such as immunization, to increase the coverage of supplementation. WHO recommends that the primary three-dose series of diphtheria, tetanus and pertussis (DTP) vaccination be administered to infants at ages 6, 10 and 14 weeks (50). WHO does not recommend vitamin A supplementation as a public health intervention to reduce infant morbidity and mortality in neonates or infants aged 1–5 months (51, 52).

In programmatic settings, infants aged under 6 months do not receive high-dose vitamin A supplementation, and the chance of co-administering high-dose vitamin A supplementation with DTP vaccination is very low. The risk is mitigated by training and the fact that vitamin A supplementation programming in low- and middle-income countries is mature. There are currently no recommendations to provide any dose of vitamin A with the DTP vaccine.

Few studies have been conducted to observe the immune response to measles-containing vaccines (MCVs) following co-administration with vitamin A supplementation (4). When 100 000 IU vitamin A supplementation was provided together with an MCV to infants aged 6–11 months, no severe adverse effects and no significant effects in enhancing the immune response were observed (53). Co-administration of vitamin A supplementation with MCV in infants aged 9 months was associated with improved immune response. The beneficial effect of combining vitamin A supplementation with measles vaccination was observed the most in non-breastfed, undernourished boys (53). It has been extrapolated that it is safe to give high-dose vitamin A supplementation with vaccines after 12 months, but the impact on child health in general of combining high-dose vitamin A supplementation with vaccines is still unknown (54).

During the WHO guidelines process, guideline group members and external experts acknowledge that co-administration of vitamin A with other health interventions, such as with vaccines, may lead to interaction with the vitamin A supplementation in infants and children aged 6–59 months and warrants further research (55–57).

WHO guidelines and recommendations on vitamin A supplementation in infants and children aged 6–59 months

The WHO guideline for vitamin A supplementation in infants and children aged 6–59 months provides global, evidenced-informed recommendations on vitamin A supplementation to prevent morbidity and mortality (17). The guideline is intended to assist Member States in choosing appropriate public health policies related to vitamin A supplementation.

Two systematic reviews served as evidence to inform this guideline. One Cochrane review reported on the effectiveness of vitamin A supplementation in preventing morbidity and mortality in children aged

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1 VigiBase is the WHO global database of individual case safety reports. In July 2019, there were over 2 million ICSRs originating in over 136 countries. The reports submitted to VigiBase generally describe no more than suspicions that have arisen from observation of an unexpected or unwanted event (49).

2 Some but not all national pharmacovigilance centres that contribute information to VigiBase make an assessment (causality assessment) of the likelihood that a medicinal product caused the suspected reaction. Information comes from a variety of sources, and the likelihood that the suspected adverse reaction is medicine related is not the same in all cases.
6–59 months (25). Another Cochrane review assessed the safety and efficacy of vitamin A supplementation relative to the reduction of morbidity and mortality in children and adults living with HIV (58).

The WHO guideline strongly recommends the provision of vitamin A supplementation to infants and children aged 6–59 months in areas experiencing vitamin A deficiency, including in populations where children may be living with HIV; these include populations in which the prevalence of night blindness is more than 1% in children aged 24–59 months and populations in which the prevalence of vitamin A deficiency is more than 20% in infants and children aged 6–59 months (17).

The guideline recommends vitamin A supplementation with one dose of 100 000 IU for children aged 6–11 months and then 200 000 IU every 4–6 months for children aged 12–59 months, as a public health intervention to reduce child morbidity and mortality (17). High-dose supplementation is administered to elevate hepatic stores and to provide vitamin A for metabolic function. The recommendation is based on the concept that vitamin A is absorbed and stored in the liver effectively in high doses and can provide a reserve during periods of low dietary intake (17).

This document, published in 2011, updated the previous guideline published in 1997 (21). The previous guideline was very similar in recommending 100 000 IU every 4–6 months for children aged 6–12 months and 200 000 IU every 4–6 months for preschool children aged over 12 months. However, the previous guideline recommended giving 50 000 IU to infants aged under 6 months, which is not currently recommended (17).

Treatment with vitamin A supplementation for children with clear or suspected xerophthalmia or measles refers to the previous guideline (21). Recommendations for children aged 6–59 months are summarized in Table 4.

Table 4. Summary of WHO recommendations on vitamin A supplementation for children aged 6–59 months

<table>
<thead>
<tr>
<th>Setting</th>
<th>Dose*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Populations with night blindness in ≥1% of children aged 24–59 months</td>
<td>100 000 IU once; 200 000 IU every 4–6 months</td>
<td>World Health Organization, 2011 (17)</td>
</tr>
<tr>
<td>Populations with prevalence of low serum retinol (&lt;0.70 µmol/L) in ≥20% of children aged 6–59 months</td>
<td>100 000 IU once; 200 000 IU every 4–6 months</td>
<td>World Health Organization, 2011 (17)</td>
</tr>
<tr>
<td>Treatment of xerophthalmia or measles</td>
<td>100 000 IU upon diagnosis, on the next day, and at least 2 weeks later; 200 000 IU upon diagnosis, on the next day, and at least 2 weeks later</td>
<td>World Health Organization, United Nations Children’s Fund and International Vitamin A Consultative Group, 1997 (21)</td>
</tr>
</tbody>
</table>

IU: international units.

* All doses are recommended as an oil-based preparation of retinyl acetate or retinyl palmitate delivered orally.

Additional evidence considerations on frequency and dosage form for the suggested supplementation scheme

Frequency

The current recommendation considers the provision of 200 000 IU every 4–6 months for children aged 12–59 months as a public health intervention to reduce child morbidity and mortality. Periodic dosing is an...
interim approach until dietary sufficiency can be found in food sources rich in preformed or provitamin A to improve vitamin A status. Frequent vitamin A supplementation is intended to prevent vitamin A deficiency and to maintain vitamin A storage during periods of increasing requirements and low intake. Periodic administration of supplements was determined to be the most feasible and cost-effective means of improving vitamin A status (21).

**Vitamin A dosage form**

Despite evidence supporting the faster absorbance of water-miscible vitamin A, the dosage form currently recommended is oil-based vitamin A capsules. Vitamin A is fat soluble and dissolving its ester in vegetable oil helps to stabilize the vitamin against oxidation. Vitamin A oil can be readily encapsulated in a gelatine shell, has been shown to retain good potency in tropical environments for an extended period of time, and does not separate as aqueous dispersions do (59).

The oil formulation of 200 000 IU vitamin A ester (palmitate), together with 40 IU of vitamin E in soft gelatine capsules is the most widely used form of dose (29). For oil-soluble high-dose vitamin A supplementation (200 000 IU), approximately 70% of vitamin A is absorbed, with 40–50% retention. Assuming that only 50% of vitamin A is retained, 200 000 IU of vitamin A will provide protection against vitamin A deficiency for approximately 240 days, depending on factors such as infection and dietary intake. The presence of infection will restrict the amount of vitamin A absorbed and retained to approximately 20–30%. Overall, 200 000 IU vitamin A supplementation will support liver stores for 60–240 days (29, 31).

**QUALITY-RELATED REGULATORY STANDARDS FOR VITAMIN A AS A MEDICAL PRODUCT**

Retinol (vitamin A) is included in both the *WHO Model List of Essential Medicines* (61) and the *WHO Model List of Essential Medicines for Children* (62). It is considered to be an essential medicine, as it addresses a high-priority health-care need of populations. Essential medicines are intended to be available within the context of functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford (61). For a medicine to be listed as essential, considerations include disease prevalence, the amount of adequate data on safety and efficacy, the availability of a good-quality form that is stable and bioavailable, and the cost effectiveness of the medicine.

The *WHO Model List of Essential Medicines for Children* describes the dosage forms and strengths of vitamin A as follows (62):

- capsule: 100 000 IU; 200 000 IU (as palmitate);
- oral oily solution: 100 000 IU (as palmitate)/mL in multidose dispenser;
- tablet (sugar-coated): 10 000 IU (as palmitate);
- water-miscible injection: 100 000 IU (as palmitate) in 2-mL ampoule.

The *WHO Model Formulary for Children* indicates vitamin A for prevention and treatment of vitamin A deficiency, for treatment of xerophthalmia caused by vitamin A deficiency, and for prevention of complications of measles (63). Orally administered vitamin A supplementation is the preferred choice for both prevention and treatment. In cases of severe anorexia, vomiting or malabsorption, vitamin A may be administered intramuscularly as a water-miscible injection (63).

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1 The term “medical products” is defined as a term that includes medicines, vaccines, diagnostics and medical devices. “Medical product” is used in this document in instead of “pharmaceutical product” (60).
The WHO Expert Committee on Specifications for Pharmaceutical Preparations has made numerous recommendations relevant to quality assurance and control (64). The guidelines and recommendations that follow are intended to give a general framework to all involved in the manufacture, regulation, procurement, distribution and importation of vitamin A capsules as a medical product, to achieve these aims more effectively.

WHO medicines quality assurance guidelines

WHO guidelines for medicines quality assurance regulate all the stages from the manufacture of vitamin A capsules as a medical product through to delivery to the population in need, thus covering production, quality control, inspection, distribution and regulatory aspects. These stages in medical product development should be regulated by national regulatory authorities, by developing national standards that include good manufacturing practices (GMP); risk analysis for production; stability testing; quality control (international specifications, sampling and laboratories); inspection of vitamin A capsule manufacturers and distribution channels; good distribution practices; good storage practices; international trade; prequalification; product registration requirements; and other quality-related guidelines. All these standards should be based on guidelines and recommendations developed by WHO or other internationally recognized institutions.

WHO good manufacturing practices for pharmaceutical products: main principles (65)

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a medical product. It is the totality of the arrangements made with the object of ensuring that medical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors. Medical products such as vitamin A capsules should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are inspected regularly by competent national, regional or international authorities. This guidance of the implementation of the GMP should be used as a standard to justify GMP status, which constitutes one of the elements of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities (65, 66). WHO provides technical support to national and regional regulatory authorities in developing their GMP standards and in the inspection of manufacturing facilities in accordance with WHO GMP or other international standards.

GMP is that part of quality management that ensures vitamin A capsules as a medical product are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification. GMP is aimed primarily at managing and diminishing the risks inherent in production of vitamin A capsules.

Such risks are essentially: contamination (the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport); cross-contamination (contamination of a starting material, intermediate product or finished product with another starting material or product during production); and mix-ups (i.e. substitution, mislabelling). Under GMP, (i) all manufacturing processes are clearly defined and systematically reviewed; (ii) qualification and validation are performed; (iii) all necessary resources are provided; (iv) instructions and procedures are written in clear and unambiguous language; (v) procedures are carried out correctly and personnel are trained to do this; (vi) records are made (manually and/or by recording instruments) during manufacture, to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations are fully recorded and investigated with the objective of determining the root cause, and appropriate corrective and preventive action is implemented; (vii) records covering manufacture and distribution are retained in a comprehensible and accessible form; (viii) proper storage and distribution of the products minimize any risk to their quality; (ix) a system is available to recall any batch of product from sale or supply; and (x) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products, to prevent recurrence (65, 66).
The necessary resources that should be provided include (i) sufficient and appropriately qualified and trained personnel; (ii) adequate premises and space; (iii) suitable equipment and services; (iv) appropriate materials, containers and labels; (v) approved procedures and instructions; (vi) suitable storage and transport; and (vii) adequate personnel, laboratories and equipment for in-process controls. A high level of sanitation and hygiene should be practised in every aspect of the manufacture of vitamin A capsules as a medical product. Potential sources of contamination should be eliminated, through an integrated comprehensive programme of sanitation and hygiene.

**WHO guidelines on quality risk management (67)**

The overall and continuing process of appropriately managing risks to product quality throughout the product’s life-cycle, in order to optimize its benefit–risk balance, is known as quality risk management.

Manufacturers of vitamin A capsules should implement a systematic process for the assessment, control, communication and review of risks to the quality of the medical product. This process should define responsibilities and the process for communicating, reporting and escalating risks involved in the manufacture of the medical product.

Risk assessment consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards, whereas risk control is a decision-making activity designed to reduce risks to an acceptable level. Risk review checks that the appropriate systems that should be in place to ensure the output of the quality risk management process are periodically monitored and reviewed, to assess new information that may impact on the original quality risk management decision. The output of the quality risk management process and associated risk analysis justifying the approach taken should be documented and endorsed by the organization’s quality unit and management. Additionally, this information should be communicated to stakeholders to keep them informed and to ensure their support (67).

**Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (68)**

The aim of these guidelines (68) is to outline the core stability data package required for registration of active pharmaceutical ingredients and finished pharmaceutical products. The purpose of stability testing is to provide evidence of how the quality of an active pharmaceutical ingredient (e.g. vitamin A oral solution) or finished pharmaceutical product (e.g. vitamin A capsules) varies with time under the influence of a variety of environmental factors, such as temperature, humidity and light. For example, retinol decomposes under accelerated degrading conditions during 10–20 days at 50 °C and 100% relative humidity (69). The stability programme also includes the study of product-related factors that influence the quality – for example, interaction of active pharmaceutical ingredients with excipients, container closure systems and packaging materials. As a result of stability testing, a retest period for the active pharmaceutical ingredient, or a shelf-life for the finished pharmaceutical product, can be established and storage conditions can be recommended (68). Various analyses have been done to identify suitable testing conditions for WHO Member States, based on climatic data, to enable each Member State to decide on long-term (real-time) stability testing conditions (70). Currently, a Policy on remaining shelf-life of medical products is being prepared (71).

**The International Pharmacopoeia (WHO)**

The activities related to The International Pharmacopoeia (72) are an essential element in overall quality control of vitamin A (retinol oral solution) supplementation, contributing to the safety and efficacy of vitamin A capsules as a medical product. In contrast to other pharmacopoeias, priority has been given for many years to medicines included in the WHO Model List of Essential Medicines (62); to medicines that are important for WHO health programmes; and to medicines that are not included in other pharmacopoeias. Since the inception of the WHO Prequalification of Medicines Team in 2001, The International Pharmacopoeia workplans also focus on medicines that are included in the team’s invitations to submit an expression of interest for product
evaluation. The ultimate goals of The International Pharmacopoeia are the promotion of good-quality medical products such as vitamin A capsules, and the development of quality control methods to assure the safety and efficacy of medical treatments worldwide. The International Pharmacopoeia provides international standards for the identification, content, purity and quality of active ingredients, medical products such as vitamin A capsules, and excipients moving in international commerce.

The International Pharmacopoeia serves as a reference to set international standards with which vitamin A capsules should comply.

According to The International Pharmacopoeia (72), paediatric vitamin A oral solution contains retinol concentrate, which is an oily form diluted in a suitable vegetable oil. The current presentations are (i) an oral oily solution in a multidose container of 100 000 IU/mL; and (ii) an oral oily solution as single doses (capsules) of 50 000 IU; 100 000 IU and 200 000 IU (73) (see Annex 1). The oral solution may also contain suitable antimicrobial agents and stabilizing agents, such as vitamin E or other antioxidants.

The Retinol oral solution monograph from the International Pharmacopoeia (73) must be interpreted in accordance with all the general requirements and testing methods, texts or notices pertaining to it. The official procedure for the development of monographs and other texts for The International Pharmacopoeia was developed and adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations and is updated regularly (74).

WHO guidelines for pharmaceutical quality control laboratories (75)

These guidelines provide advice on the quality management system within which the analysis of active pharmaceutical ingredients (e.g. vitamin A oral solution), excipients and medical products (e.g. vitamin A capsules) should be performed to demonstrate that reliable results are obtained. The recommended good practices range from organizational structure and staffing to advice on routines and management; materials, equipment, instruments and other devices; working procedures; safety; documentation requirements; and evaluation of test results (75).

WHO guidelines for sampling of pharmaceutical products and related materials (76)

A sample is a portion of a material collected according to a defined sampling procedure. The size of any sample should be sufficient to allow all anticipated test procedures to be carried out, including all repetitions and retention samples. The WHO guidelines for sampling of pharmaceutical products and related materials comprise the operations designed to select a portion of a medical product such as vitamin A capsules for a defined purpose. The sampling procedure should be appropriate to the purpose of sampling, to the type of controls intended to be applied to the samples, and to the material to be sampled.

All operations related to sampling should be performed with care, using proper equipment and tools. Any contamination of the sample by dust or other foreign material is liable to jeopardize the validity of the subsequent analyses (76).

Guidelines on inspection of pharmaceutical manufacturers (77–80)

Inspections are part of the overall quality assurance system. These guidelines cover inspection of the production and control of final dosage forms of medical products such as vitamin A capsules, and of active pharmaceutical ingredients employed in their manufacture. The objective of inspecting pharmaceutical manufacturing facilities is either to enforce GMP compliance or to provide authorization for the manufacture of vitamin A capsules as a medical product, usually in relation to an application for marketing authorization or exportation. The government inspectorate represents the enforcement arm of the national regulatory authority. Its function is to ensure adherence by manufacturers to all licensing provisions, and specifically to GMP. A further aspect of pharmaceutical inspection is monitoring the quality of vitamin A capsules in distribution channels, from the point of manufacture to delivery to the recipient, as a means of eliminating any
potential hazards (81). Other WHO inspection guidelines include Guidance on good manufacturing practices: inspection report (77), Guidelines on pre-approval inspections (78), Quality systems requirements for national good manufacturing practice inspectorates (79), and Model certificate of good manufacturing practice (80).

WHO good distribution practices for pharmaceutical products (82)

Distribution is an important activity in the integrated supply-chain management of medical products. All parties involved in the distribution of vitamin A capsules as a medical product have a responsibility to ensure that the quality of the product and the integrity of the distribution chain are maintained throughout the distribution process, from the site of the manufacturer to the entity responsible for dispensing or providing vitamin A capsules to the population in need. The distribution process includes, but is not limited to, procurement, purchasing, storage, distribution, transportation, repackaging, relabelling, documentation and record-keeping.

The good distribution practices set out appropriate steps to assist in fulfilling the responsibilities involved in the different aspects of the distribution process within the supply chain, to preserve the quality of the product and to avoid the introduction of counterfeits into the marketplace via the distribution chain. Although high-dose vitamin A supplements are not easily falsified, if counterfeit vitamin A capsules are found in the distribution chain, they should be kept apart from other medical products, to avoid any confusion. Also, they should be clearly identified and separated from stock that is intended for sale or distribution, and national regulatory authorities and the holder of the marketing authorization for the original product should be informed immediately.

Good distribution practices should be considered for implementation by, among others, governments, regulatory bodies, international procurement organizations, donor agencies, certifying bodies, and all parties involved in any aspect of the trade and distribution of vitamin A capsules, including health-care workers. Every activity in the distribution of vitamin A capsules as a medical product should be carried out according to the principles of GMP, good storage practices and good distribution practices, as applicable (82).

Guide to good storage practices for pharmaceuticals (83)

The objective of this guide is to describe the special measures considered appropriate for the storage and transportation of pharmaceuticals. However, they may be adapted to meet individual needs where necessary, provided the desired standards of quality are still achieved. These guidelines should be adjusted in line with the type of activity where the storage of pharmaceuticals is taking place.

Storage conditions for medical products and materials should be in compliance with the labelling, which is based on the results of stability testing. Good storage practices for medical products include provisions for personnel, premises and facilities, storage requirements, returned goods, dispatch and transport, and product recall (83).

Note: A revision of the good distribution practices (see “WHO good distribution practices for pharmaceutical products” (82)) and good storage practices (see “Guide to good storage practices for pharmaceuticals” (83)) is currently under way. The proposal is to possibly merge the two guidance texts into one: good storage and distribution practices.

Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (84)

The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce was developed by WHO in response to the request of Member States to facilitate international trade in medical products between Member States. These guidelines give guidance to the issuing and requesting health authorities (84).1

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1 A proposal for revision of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce is currently under way (85).
The scheme is an administrative instrument that requires each participating Member State, upon application by a commercially interested party, to attest to the competent authority of another participating Member State that (i) a specific product such as vitamin A capsules is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded; (ii) the plant in which it is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP; and (iii) all submitted product information, including labelling, is currently authorized in the certifying country.

The scheme is based on the concept of sharing of responsibilities between three partners: (i) the pharmaceutical manufacturer in the exporting country has to produce the vitamin A capsules in accordance with GMP; (ii) the medicine regulatory authority of the exporting country has to inspect the manufacturing plant to confirm that it complies with GMP; and (iii) the medicine regulatory authority of the importing country has to request from its counterpart in the exporting country information on the regulatory status of the vitamin A capsules intended for import, and confirmation that the manufacturer complies with GMP standards. In normal circumstances, the certified information issued by the medicine regulatory authority in the exporting country reaches the medicine regulatory authority of the importing country via the manufacturer, exporter or importer and is used as the basis for medicine registration in the importing country. A country wishing to participate in the scheme must notify WHO of its intention to do so. The country must define both the extent to which it wishes to participate and the authority that is competent to issue or receive information as provided for in the scheme. Three documents can be requested within the scope of the scheme: Certificate of Pharmaceutical Product (product certificate), Statement of licensing status of pharmaceutical product(s), and Batch certificate of pharmaceutical product. See the full guidelines for more information on the implementation of the scheme and instructions on how to complete these certification forms (84).

Procedure for prequalification of pharmaceutical products (86)
Prequalification ensures that active pharmaceutical ingredients and finished pharmaceutical products are safe and meet stringent quality standards. For each product type, prequalification is based on application of unified standards of quality, safety and efficacy or performance to product dossier assessment; an inspection of the corresponding manufacturing sites; and other product-specific elements of evaluation.

As high-dose vitamin A supplements are not easily counterfeit and the oral solution is not considered a high-risk substance, these supplements are currently not part of the WHO prequalification programme. However, any manufacturer of vitamin A oral solution or vitamin A capsules can express an interest in having its active pharmaceutical ingredients or finished pharmaceutical product evaluated by WHO, provided those products are eligible for assessment.

The following is a simplified overview of the prequalification process for active pharmaceutical ingredients and finished pharmaceutical products: (i) the manufacturer verifies that the active pharmaceutical ingredient or finished pharmaceutical product that wants to submit for evaluation for prequalification is included in the relevant invitation to manufacturers to submit an expression of interest for evaluation; (ii) the manufacturer submits an application to WHO in accordance with the prequalification procedure for the product (active pharmaceutical ingredient or finished pharmaceutical product); (iii) WHO reviews the information submitted for evaluation for prequalification – this review may include a request for additional information, inspection of the manufacturing site and, if relevant, the identity of the contract research organization that performed a related study may also be necessary; (iv) if the active pharmaceutical ingredient or finished pharmaceutical product has already been approved by a stringent regulatory authority, the applicant may choose to make a submission for abbreviated assessment (86).

Active pharmaceutical ingredients and finished pharmaceutical products that meet assessment and inspection criteria are added to the WHO lists of prequalified active pharmaceutical ingredients and prequalified medicinal products.
Product registration requirements

The existence and functioning of a comprehensive medicines regulatory system supported by legislation is a prerequisite for an overall quality assurance system. The most important starting point for imported products is the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. This gives basic information on composition, an assurance that the product is manufactured in accordance with GMP in premises subject to inspection, and information on the regulatory status of the product in the country of export. A certificate, issued in compliance with the model format recommended by WHO, should be required whenever application is made to license an imported product. It is anticipated that once the initial marketing authorizations have been made, the registration process can be administered effectively if due advantage is taken of the scheme (64).

In many countries with limited regulatory resources, marketing authorization of finished pharmaceutical products such as vitamin A capsules can take considerable time. In some cases, this time can extend to two or more years, meaning that children may not receive treatment that could save their lives or improve their state of health. WHO has reacted to this situation by (i) creating a collaborative procedure to facilitate the assessment and accelerated national registration of WHO prequalified finished pharmaceutical products; and (ii) creating a collaborative procedure to accelerate registration of finished pharmaceutical products that have already received approval from a stringent regulatory authority (66).

Vitamin A finished product specifications

The following section provides a summary of the technical specifications and manufacturing process that manufacturers of vitamin A capsules may be required to meet in order to succeed in a prequalification process.

Nutrition International and UNICEF have procured vitamin A capsules for more than two decades to ensure the supply of supplements for the global vitamin A programmes. Annex 3 includes, as an example, the technical product specifications developed by these two entities to prequalify their manufacturers of high-dose vitamin A capsules (87).

The vitamin A capsule finished product is an oil-based vitamin A preparation encapsulated in a soft gelatine capsule designed to be used as a single-dose dispenser in public health programmes worldwide. Vitamin A soft gelatine capsules must be manufactured to comply with The International Pharmacopoeia monograph on Retinol oral solution (73) or the United States Pharmacopeia vitamin A oral liquid preparation monograph (88) (see Annexes 1, 2 and 3).

Product formulation

Product formulation components and finished product specifications for vitamin A oral formulation soft gel capsules are listed in Table 5 and described next (87, 89).

Table 5. Product formulation and identification of vitamin A oral formulation soft gel capsules

<table>
<thead>
<tr>
<th>Target group</th>
<th>Dosage of active pharmaceutical ingredient</th>
<th>Capsule gel colour (Code colour)</th>
<th>Other ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants aged 6–11 months</td>
<td>100 000 IU (30 mg retinol palmitate)</td>
<td>Blue (PMS 302c)</td>
<td>Vitamin E (dl-alpha-tocopherol or tocopheryl acetate) as antioxidant, soybean oil, gelatine capsule (gelatine, glycerine, ethyl vanillin, colouring agents)</td>
</tr>
<tr>
<td>Children aged 12–59 months</td>
<td>200 000 IU (60 mg retinol palmitate)</td>
<td>Red (PMS 187c)</td>
<td></td>
</tr>
</tbody>
</table>

IU: international units.
Dosage form

The soft gelatine capsule filled with vitamin A is used as a dropper to deliver the oily liquid contents into a child’s mouth. For optimal use, the capsule must have a narrow end (tip), which is cut with scissors before administration of the dose. The capsule should be large enough to hold between the thumb and index finger once the tip is cut. The capsule is then squeezed to express the entire liquid contents of the capsule (the measured dose of vitamin A) into the child’s mouth.

Capsule hardness

The soft gelatine capsule is not swallowed but rather is used as a dropper to deliver the liquid contents directly into the recipient’s mouth. The capsule shell must be hard enough to withstand hot and humid field conditions (i.e. must not leak or clump with other capsules) and soft enough to be used as a dropper so 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). Capsules must not be brittle (i.e. must not break or crack at the seal when squeezed). In light of these considerations, manufacturers must set their own minimum and maximum hardness limits for stability trials and point of release, as measured by a hardness tester.

Dosage strengths

Vitamin A capsules come in two WHO-recommended strengths according to the child’s age: 100 000 IU for children aged 6–11 months and 200 000 IU for children aged 12–59 months. Children living with HIV receive the same age-appropriate dosage as their HIV-negative peers. The strength of the capsule is signified by its colour as shown, in Table 5.

Ingredients

Vitamin A (active pharmaceutical ingredient)

Vitamin A oral liquid preparation is the active pharmaceutical ingredient in the finished product and is manufactured as a medical product, owing to the high dosage (87). Retinyl palmitate is the form of vitamin A used in the global in-kind assistance programme, owing to its wider commercial availability; however, retinyl acetate and retinyl propionate are other available forms of oil-based vitamin A. The 100 000 IU dose of vitamin A contains 30 mg of retinol palmitate; the 200 000 IU dose contains 60 mg of retinol palmitate.

The active pharmaceutical ingredient manufacturer should comply with GMP for pharmaceutical-grade products. Evidence of GMP compliance should be demonstrated.

The assay method used to determine vitamin A levels in the finished product should comply with the descriptions in The International Pharmacopoeia monograph on Retinol oral solution (73) or the United States Pharmacopeia vitamin A oral liquid preparation monograph (88) (see Annexes 1 and 2). Evidence of method specificity and precision should be demonstrated. Vitamin A assay test results should confirm a value between 90.0% and 120.0% of the labelled amount of Vitamin A.

Vitamin E (antioxidant)

Vitamin A for capsules is diluted in a high-quality vegetable oil together with vitamin E. Two primary functions of vitamin E have led to adding it to high-dose vitamin A supplementation: it acts as a lipid-soluble antioxidant, and it provides cell membrane stability. Owing to these functions, vitamin E has been shown to increase storage and absorption of vitamin A, while alleviating the effects of hypervitaminosis A (90–92).

As a lipid-soluble antioxidant, vitamin E inhibits propagation of free radicals in membranes and lipoproteins. This can lead to increased storage of vitamin A in the liver by providing protection to vitamin A in the intestine, especially when the dietary intake has a high content of unsaturated fat (93), and by protecting vitamin A in target tissues. Numerous animal studies in rats, chickens and dogs have demonstrated improved
absorption and storage of vitamin A when vitamin E is present, compared to no vitamin E or vitamin E-depleted conditions (91, 92). Further, vitamin A is poorly retained in vitamin E-depleted conditions, which could lead to acute secondary vitamin A deficiency due to decreased retention after absorption (94). One human study found increased plasma retinol with vitamin E administration alone in both vitamin A-sufficient and vitamin A-deficient children (95). Another human study giving 30 000 IU of vitamin A daily found the addition of 200 IU of vitamin E reduced serum vitamin A, while maintaining plasma retinol-binding protein and transthyretin, hypothesized to indicate increased delivery of vitamin A to target tissues (96).

The mechanism of how vitamin E may decrease symptoms of hypervitaminosis A is still unknown, but it may be caused by the ability of alpha-tocopherol to function in stabilizing and protecting biomembranes by assisting in molecular packing of phospholipids (92, 97, 98). Owing to minor side-effects seen in human vitamin A supplementation trials without vitamin E (45, 46), addition of 40 IU of vitamin E to 200 000 IU of vitamin A was efficacious for xerophthalmia and maintenance of serum retinol, while avoiding the side-effects of vitamin A (91).

The amount of vitamin E in the capsule of vitamin A is higher than the adequate intake for infants aged 7–12 months (5 mg) and the estimated average requirement for children aged 1–3 years (5 mg) and 4–8 years (6 mg), but it is still below the upper limits of 200 mg for children aged 1–3 years and 300 mg for children aged 4–9 years (99). Ultimately, the addition of vitamin E to vitamin A supplementation has been suggested, owing to the likely effects of increasing the efficacy and safety of vitamin A supplementation with no side-effects of its own (21, 39, 91, 92, 100).

The Nutrition International and UNICEF technical product specification includes Vitamin E as a non-therapeutic support agent and antioxidant for vitamin A capsules (88). This specification requires 20 IU of vitamin E to stabilize a 100 000 IU dose of vitamin A, and 40 IU of vitamin E to stabilize a 200 000 IU dose of vitamin A, for a 36-month shelf-life (see Annex 3). The acceptable forms of vitamin E are dl-alpha-tocopherol and tocopheryl acetate.

Adding vitamin E to a high-dose vitamin A supplement increases the bioavailability of vitamin A, ensuring the body properly utilizes the administered vitamin A. Vitamin E also has a protective effect on cell membranes, which lessens the chance of hypersensitivity to administration of high-dose vitamin A (39). These properties justify the addition of vitamin E to high-dose vitamin A supplements.

Vitamin E performance and quality are verified by manufacturers, which monitor the stability of vitamin E throughout the product’s shelf-life (as part of stability programmes) and by measuring vitamin E levels at the point of release, as indicated on the certificate of analysis. The International Pharmacopoeia retinol oral solution monograph (73) and the United States Pharmacopeia vitamin A oral liquid preparation monograph (88) do not specify vitamin E acceptance limits, although The International Pharmacopoeia monograph does refer to the use of antioxidants (73). Unless otherwise justified, the vitamin E specification range should reflect the tighter range set for vitamin A.

**Gelatine**

Gelatine is used to make the soft-capsule single-dose container to hold the vitamin A oily liquid. The gelatine is usually mixed with other ingredients such as glycerol or another plasticizer, to give the shell its soft and elastic properties, required for the Nutrition International and UNICEF technical product specification on hardness. The capsules must be free of preservatives such as parabens. All gelatine used for the capsules must be manufactured to meet the criteria described in the latest edition of the United States Pharmacopeia (101), The International Pharmacopoeia (72) or the European Pharmacopoeia (102).

Gelatine can be of cow, pig, fish or vegetable origin. Bovine- or porcine-based materials are commonly used to manufacture soft gelatine capsules in the pharmaceutical industry. High-dose vitamin A capsules have not used vegetable- or fish-based gelatines because of their sensitivity to temperature; to date, they do not provide the same level of protection to the active pharmaceutical ingredient as animal-based gelatine.
Gelatine manufacturers must provide evidence that their gelatine is free from bovine spongiform encephalopathy (which leads to Creutzfeldt–Jakob disease in humans), although there is no evidence that this is transmitted through gelatine. A certificate of conformity can be issued to the gelatine manufacturer by the European Directorate for Safety of Medicines, to provide this evidence.

The gelatine capsules are used only as dispensers and are not swallowed; however, halal certification can be requested in specific countries or settings.

**Colouring**

The Nutrition International and UNICEF technical product specification includes precise colour references for the dosage forms (87). Health workers worldwide have been trained to associate the blue capsule with the lower dose (100,000 IU for children aged 6–11 months) and the red capsule with the higher dose (200,000 IU for children aged 12–59 months). Field-training materials reflect this distinction. It is strongly recommended that capsules colour-match the appropriate internationally recognized code colour provided in Table 5.

The capsules must be opaque, to protect the vitamin A fill from sunlight. Over-exposure to sunlight, which can occur if capsules are removed from their container for an extended period of time, can cause vitamin A to become inactive.

**Flavour**

Ethyl vanillin should be added to the shell or fill as a flavouring agent, to mask the unpleasant smell associated with the gelatine. Vanillin has been used successfully for a number of years in the global vitamin A capsule donation programme, with no documented complaints.

**Packaging and labelling**

**Packaging**

Nutrition International and UNICEF technical specifications for vitamin A capsule packaging (87) (see Annex 3) may require that the manufacturer demonstrates their container closure system, including primary packaging materials such as containers, closures and seals, meets the pharmaceutical container standards of a recognized pharmacopoeia. The container closure system should protect the vitamin A capsule from factors that cause degradation in their quality over their shelf-life, such as light, heat, oxygen and moisture. Vitamin A capsule packaging should be suitable for shipment, storage and use worldwide at elevated temperatures and humidity, as described in the section "Shelf-life, storage and stability". All packaging components should be tested against acceptable criteria to determine suitability.

Vitamin A capsules should be kept in opaque containers that can be closed tightly to minimize light transmission and humidity. Humidity can be further minimized by using containers with a low rate of water vapour permeation and sufficient desiccant material. A seal is recommended, to prevent microbial contamination and make the container tamper-evident. The bottle size should be proportional to the content, to limit the opportunity for oxidation.

**Desiccant**

A desiccant pack must be included in the capsule containers, to prevent capsules from softening and clumping due to moisture in tropical climates. Desiccants are considered primary packaging components and should differ in shape and size from the vitamin A soft gelatine capsules in the bottle.

**Secondary packaging**

Secondary packaging should be strong enough to resist crushing during transportation and storage, in order to maintain the product’s suitability for intended use throughout its stated shelf-life.
Labelling

Although the vitamin A capsules are considered the primary containers, they are exempt from the requirements of individual labelling, owing to their small size. Therefore, the bottle (technically the secondary container) must be labelled appropriately and must include at least the following information: medicine name, quantity, strength, manufacturer name, lot number, expiration date and directions for use. Statements and labelling must comply with the relevant pharmacopoeia standards.

Quality management system at the manufacturing site

Pharmaceutical activities should be carried out in line with national, regional or international regulations. Fig. 1 is a generic representation of steps in the manufacturing and control process for vitamin A that can serve as a guidance to define the appropriate GMP.

Fig. 1. Generic manufacturing and control process for vitamin A capsules
Manufacturers should have in place a quality management system covering all matters that individually or collectively influence the quality of a product (65). Two essential elements are necessary: (i) an infrastructure for quality that encompasses organizational structure, procedures, processes and resources; and (ii) systematic actions that ensure confidence that a product or service will meet quality requirements.

These elements may be met by establishing teams that share responsibility for quality systems (e.g. quality control, quality assurance, regulatory affairs, validation departments) and by establishing documentation systems (e.g. quality manuals, standard operating procedures, batch production records). Quality management incorporates GMP, quality risk management and other factors.

Quality compliance includes responsibility for standard operating procedures, master batch production records, change control systems, customer complaint administration, quality agreements, auditing systems, GMP training, annual product reviews, and the vendor qualification programme. Raw-material and component vendors may be qualified by undergoing GMP assessment via site audits, questionnaires or external audits.

The department in charge of quality assurance manages product investigations following nonconformance events, complaint investigations, returned goods, or out-of-specification results. Quality assurance involves review of manufacturing documents for completion and responsibility for product release, after reviewing that certificates of analysis for each batch meet technical specifications and verifying that all products have been manufactured in compliance with current GMP standards and according to organizational standard operating procedures.

The department in charge of regulatory affairs is involved in maintenance of licences and marketing authorization (registration). The department liaises with regulatory agencies, customers and suppliers. It is involved when changes are needed to supplied components, registered products or intermediates, to ensure product development and post-approval changes are conducted and documents supplied according to applicable guidelines.

A quality control unit performs the physical and chemical tests required to verify or monitor the quality of raw materials and finished products. This unit is often involved in stability testing and quality investigations.

A team should be responsible for administering a validation master plan that encompasses validation considerations related to facilities, equipment, utilities, computer systems and software, processes, analytical methods and cleaning methods.

Manufacturer certifications, licences and marketing authorization

Manufacturers may be required to provide the following certifications, licences and marketing authorization (registration) to show their compliance with stringent manufacturing standards:

- marketing authorization in the country of manufacture; where this cannot be provided immediately, the manufacturer must submit a letter committing to obtaining domestic registration status. The manufacturer must also provide any documentation requested by the importing country for in-country product registration that may be required to receive the goods;
- certificate of pharmaceutical product, according to the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce or an equivalent, issued by the national regulatory authority;
- certificate of GMP; vitamin A oral liquid preparation is the active ingredient in the vitamin A capsule finished product and is considered a medical product, owing to the high dosage. The active pharmaceutical ingredient used in the capsules must be manufactured and handled according to GMP standards for medical products, as certified by national medicine regulatory authorities or an internationally recognized authority that is a member of or partner to the Pharmaceutical Inspection Co-operation Scheme;
- certificate of suitability to demonstrate that vitamin A, vitamin E and gelatine used in the vitamin A capsules have been manufactured to meet pharmacopoeia standards; and
- (in some destination countries), halal certification by an internationally recognized certifying body; this requirement applies to the finished pharmaceutical product and excipient manufacturers involved in the manufacturing process.

**Shelf-life, storage and stability**

This section is not comprehensive and should be read in conjunction with the WHO guidelines on stability testing (68), the ICH harmonised tripartite guideline: evaluation for stability data Q1E (103), and the Guidance for industry: Q1E evaluation of stability data (104).

Shelf-life is the length of time a product may be stored without affecting its usability, safety, purity or potency. It is the period during which the vitamin A oral liquid preparation is expected to remain with the specification of 90.0–120.0% of stated label claim, provided the product is stored under the conditions specified on the label.

Nutrition International and UNICEF require that manufacturers demonstrate the shelf life of the product for up to 36 months (demonstrated by long-term stability data). However, a 2-year shelf life may be considered sufficient for a country-level programme. A shelf-life of less than 2 years is not advised, as it may result in unnecessary product wastage. The assigned shelf-life and recommended storage conditions should reflect the outcome of stability studies and be printed on the labels. Shelf-life requirements are determined by supply-chain logistics, delivery mechanisms, budgets and economies of scale.

Product shelf-life must be demonstrated using stability data generated from studies under appropriate climatic conditions. For example, if a country identifies with zone IVa climatic conditions, then the country would request evidence that products are stable in those particular climatic conditions (69).

Vitamin A oral liquid preparation exhibits unstable degradation behaviour, as demonstrated by a significant change of 5% or more in assay from its initial content (68). It is difficult to assume that the degradation relationship observed from long-term data will continue to apply beyond the observation period because of the nature of the degradation and the high variability in the vitamin A assay sample-preparation method. No statistical model has accurately predicted shelf-life, and the use of statistical models to extrapolate shelf-life is not recommended. Shelf-life should be supported using actual data (i.e. a 36-month shelf-life should be supported by 36 months of real data).

The minimum data requirements to claim a 3-year shelf-life are 36 months of long-term stability data from at least three primary batches, using stability testing protocols for the climatic conditions specified. Shelf-life compliance should be demonstrated using a high-performance liquid chromatography assay method to measure vitamin A. Primary batches should have the same formulation and packaging as proposed for marketing. The manufacturing process for primary batches should simulate regular production batches and should provide a product of the same quality and meeting the same specifications as that intended for marketing. Each primary batch should be at minimum pilot scale (one-tenth of a full production batch) and ideally should be manufactured using different batches of the active pharmaceutical ingredient.

A systematic approach to the presentation and evaluation of stability data should be adopted, including (as appropriate) results of physical, chemical, biological and microbiological tests (including particular attributes of the dosage form such as capsule hardness). Stability study reports should include specific quality attributes that will be evaluated; testing methodology; and acceptance criteria. See Annex 3 for sample minimum information requirements to be included in stability testing protocols and reports that manufacturers of vitamin A capsules are required to meet in order to prequalify through the Nutrition International and UNICEF expression of interest for vitamin A capsules (87).
Ongoing quality monitoring

Quality continues to be verified upon receipt of goods at distribution centres, to ensure the product and packaging meet requirements. A randomly selected sample of batches should be tested by an accredited third-party laboratory. For new manufacturers, the product should not be released for further distribution until acceptable batch test results are reported.

CLOSING REMARKS AND KNOWLEDGE GAPS

Vitamin A deficiency continues to present a major public health challenge globally, particularly in low- and middle-income countries. Deficiency heightens susceptibility to morbidity and mortality, particularly for children aged 6–59 months. Combined evidence continues to support the protective effect of vitamin A supplementation against all-cause mortality for vitamin A-deficient children between 6 and 59 months of age, as well as cause-specific mortality due to diarrhoea, measles and lower respiratory tract infections. Where vitamin A supplementation is prevalent, it exerts a protective effect against the sequelae of xerophthalmia, night blindness, and Bitot spots.

WHO guidelines for medicines quality assurance regulate all the stages of medical products such as vitamin A capsules from the manufacture to the delivery to the population in need, thus covering production, quality control, inspection, distribution and regulatory aspects. These stages should be regulated by national regulatory authorities, by developing national standards that include GMP; risk analysis for production; stability testing; quality control (international specifications, sampling and laboratories); inspection of vitamin A capsule manufacturers and distribution channels; good distribution practices; good storage practices; international trade; prequalification; product registration requirements; and other quality-related guidelines.

The need for further research on specific areas of vitamin A supplementation in infants and children aged 6–59 months has been acknowledged in the current WHO guideline (17), such as the effect of different doses of vitamin A on the critical outcomes of morbidity and mortality, and stratification of the data by sex, length of follow-up, and subsequent vitamin A supplementation. Other areas for further research are the co-interventions that may interact with vitamin A, such as other nutrients (e.g. vitamin D) and vaccines (e.g. DTP); and risk of excessive intake in coexisting public vitamin A programmes. As the vitamin A global landscape continues to change, continued surveillance, monitoring and evaluation of vitamin A supplementation programmes, including their production and the vitamin A status of population groups of interest, will be essential to ensure vitamin A supplementation is properly targeted and effective.
REFERENCES


ANNEX 1

The International Pharmacopoeia retinol oral solution monograph (73)

Retinol oral solution (Retinoli solutio peroralium)
Other name: Paediatric vitamin A oral solution; vitamin A oral solution.

Category: Vitamin.

Storage: Paediatric retinol oral solution should be kept in a tightly closed container, protected from light.

Labelling: The labelling should state the name of the retinol ester or esters present, the content of vitamin A expressed in International Units (IU) for single doses or IU/mL for multidose containers, and the names and quantities of any stabilizing agents added.

Additional information

Strength in the current WHO Model list of essential medicines:
Oral oily solution in multidose container: 100 000 IU/mL.
Oral oily solution as single doses ("capsules"): 50 000 IU; 100 000 IU; 200 000 IU.

Strength in the current WHO Model list of essential medicines for children:
Oral oily solution in multidose container: 100 000 IU/mL.
Oral oily solution as single doses ("capsules"): 100 000 IU; 200 000 IU.

Requirements

Complies with the monograph for "Liquid preparations for oral use".

Definition. Retinol oral solution contains Retinol concentrate, oily form diluted in a suitable vegetable oil. It may contain suitable antimicrobial agents and stabilizing agents (such as vitamin E or other antioxidants). The oral solution contains not less than 90.0% and not more than 120.0% of the amount of vitamin A stated on the label.

Retinol oral solution may be presented either in a multidose container with a suitable administration device or as single doses, each encapsulated in a soft gelatin shell. The "capsule" shell is designed so that it may be broached (for example, with a nipple which may be cut) and so that the oral solution may be administered easily by mouth when the broached shell is squeezed gently. The capsule shell constitutes the single unit container.

Manufacture. For an oral solution presented as single doses, each encapsulated in a soft gelatin shell, the composition and method of manufacture of the soft gelatin shell and the packaging of the final product is chosen and validated to ensure that the contents can be adequately expressed with use of only gentle pressure.

Carry out the analytical procedures as rapidly as possible, avoiding exposure to actinic light and oxidizing agents, oxidizing catalysts (e.g. copper, iron, etc.), acids, heat and maintaining whenever possible an atmosphere of nitrogen above the solutions.

Identity tests

- Either tests A and B or tests A and C may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R8 as the coating substance and a mixture of 12 volumes of cyclohexane R and 1 volume of ether R as the mobile phase. Apply separately to the plate 2 μl of each of the following solutions in cyclohexane R. For solution (A) dissolve a quantity of the oral solution containing the equivalent of 50 000 IU of vitamin A in 10 mL. For solution (B) prepare a solution of retinol esters R3 containing the equivalent of 5000 IU of vitamin A per mL of each ester (retinol acetate, retinol propionate, and retinol palmitate). After removing the plate from the chromatographic chamber, allow it to dry in air, and examine the chromatogram in ultraviolet light (254 nm).

The principal spot or spots obtained with solution (A) corresponds or correspond in position and appearance to one or more of the spots obtained with solution (B) in accordance with the ester content stated on the label. The test is not valid unless the chromatogram obtained with solution (B) shows three clearly separated spots. The Rf values of the esters increase in the following order: retinol acetate, retinol propionate, retinol palmitate.

B. See the test described below under Assay method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. To a quantity of the oral solution containing the equivalent of 50 000 IU of vitamin A, add 100 mL of ethanol (~750 g/l) TS. Dilute 1 mL of the resulting solution to 50 mL with a mixture of 100 volumes of ethanol (~750 g/l) TS and 1 volume of hydrochloric acid (~420 g/l) TS. Immediately after preparation measure the absorbance (1.6) in the range 300 to 400 nm. The solution exhibits a single maximum at 326 nm. Heat the solution in a water-bath for 30 seconds and cool rapidly. The absorption spectrum of the resulting solution, when observed between 300 and
- 400 nm, exhibits a shoulder at 332 nm and maxima at 348, 367 and 389 nm.

**Uniformity of deliverable dose (single-dose containers).** For an oral solution presented in single-dose containers the individual mass of the expressed contents of at least 18 of the single-dose containers as weighed under Assay is within ± 10% of the average mass and no individual mass is outside ± 20%.

**Assay**

For an oral solution presented in single-dose containers express the contents of 20 single-dose containers, following the directions for use as stated on the label. Weigh directly the individual contents delivered from each single-dose container and calculate the average mass. (Do not weigh the contents delivered by difference between full and empty containers.) Carry out the assay using the mixed oral solution from the 20 containers.

- Either method A, where valid, or method B may be applied.

**A.** Immediately dissolve a quantity of the oral solution containing the equivalent of about 200 000 IU of vitamin A, accurately weighed, in 5 mL of n-pentane R and dilute with 2-propanol R to a presumed concentration of 10-15 IU per mL. Verify that the absorption maximum of the solution to be examined, against 2-propanol R as blank, lies between 325 nm and 327 nm. Measure the absorbances at 300 nm, 326 nm, 350 nm and 370 nm. Calculate the ratio $A_{326}/A_{325}$ for each wavelength. If the ratios do not exceed 0.60 at 300 nm, 0.54 at 350 nm and 0.14 at 370 nm, calculate the content of vitamin A in IU.

For an oral solution presented in a multidose container calculate the content of vitamin A in IU per mL from the expression: $A_{326} \times V \times d \times 1900 / (100 \times m)$, where $A_{326}$ is the absorbance at 326 nm, $V$ is the dilution factor used to give 10-15 IU per mL, $d$ is the length of sample used in g, $m$ is the weight per mL (1.3.1) of the oral solution and 1900 is the factor to convert the specific absorbances of esters of retinol into IU per g.

For an oral solution presented as single doses calculate the deliverable content of vitamin A in IU per “capsule” from the expression: $A_{326} \times V \times AM \times 1900 / (100 \times m)$, where $A_{326}$ is the absorbance at 326 nm, $V$ is the dilution factor used to give 10-15 IU per mL, $m$ is the mass of sample used in g, $AM$ is the average mass of the expressed contents in g per “capsule” and 1900 is the factor to convert the specific absorbencies of esters of retinol into IU per g.

If one or more of the ratios $A_{326}/A_{325}$ exceeds the values given, or if the wavelength of the absorption maximum does not lie between 325 nm and 327 nm, use Method B.

**B.** Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with octadecylsilane groups (5 μm). As the mobile phase use a mixture of 95 volumes of methanol R and 5 volumes of water R.

Prepare the following solutions. For solution (1) transfer a quantity of the oral solution containing the equivalent of about 100 000 IU of vitamin A, accurately weighed, into a 100 mL volumetric flask. Dissolve immediately in 5 mL of n-pentane R. Add 40 mL of 0.1 M tetraethylammonium hydroxide TS in 2-propanol R. Swirl gently and allow the mixture to stand for 10 minutes at a temperature between 60 °C and 65 °C, swirling occasionally. Allow to cool to room temperature, dilute to volume with 2-propanol R containing 1 g/L butylated hydroxytoluene R, and homogenize carefully to avoid air-bubbles. Dilute 5 mL of the resulting solution to 50 mL with 2-propanol R. For solution (2) transfer an amount of retinol acetate RS containing the equivalent of about 100 000 IU of vitamin A, accurately weighed, into a 100 mL volumetric flask. Proceed as described for solution (1).

Operate with a flow rate of 1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 325 nm.

Inject alternately 10 μL of solutions (1) and (2) and record the chromatograms for 1.5 times the retention time of retinol.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per mL (1.3.1) and calculate the content of vitamin A in IU per mL of the oral solution or, where appropriate, in IU delivered per “capsule”.
Vitamin A Oral Liquid Preparation

Definition

Change to read:

Vitamin A Oral Liquid Preparation is an emulsion, suspension, or solution that contains retinyl acetate or retinyl palmitate in an amount equivalent to NLT 15 μg/mL retinyl acetate and NMT 20.0% of the labeled amount of vitamin A, as retinol (C₂₂H₃₀O).”

Identification

[Note: Use low-alkaline glassware.]

A. Sample solution: Prepare a solution in methylene chloride containing an amount of Oral Liquid Preparation equivalent to about 6 μg of retinyl acetate in 1 mL.

Analysis: Add 10 mL of methylene chloride to 1 mL of Sample solution.

Acceptance criteria: A translucent blue color appears at once.

B. Thin-layer Chromatographic Identification Test

[2010]

Standard solution: 0.5 mg/mL of retinol from USP Retinyl Acetate RS or USP Retinyl Palmitate RS in methylene chloride.

Sample solution: Dilute or extract with methylene chloride a quantity of Oral Liquid Preparation to obtain a solution with a nominal concentration of 0.5 mg/mL of retinyl acetate.

Application volume: 10 μL as an 8-mm band

Developing solvent system: A mixture of cyclohexane and ethyl acetate (4:1).

Spray reagent: 0.2 g/mL of phosphomolybdic acid in alcohol, filter, and use only the clear filtrate.

Analysis: Apply the Sample solution at the starting point of the chromatography, and proceed as directed in Chromatography (621). Thin-Layer Chromatography. Allow the solvent front to move 10 cm. Remove the plate, and air-dry. Spray with Spray reagent.

Acceptance criteria: The blue-green spot formed is indicative of the presence of retinyl acetate, and Rf & value corresponds to that of the Standard solution. The approximate Rf values of the prominent spots, corresponding to the different forms of retinyl acetate, are 0.6 for the alcohol form, 0.45 for the acetate, and 0.7 for the palmitate.

Assay

Change to read:

A. Vitamin A

[Note: Use low-alkaline glassware.]

Mobile phase: n-Hexane

Standard solution 1: 10 μg/mL of retinyl acetate from USP Retinyl Acetate RS in n-Hexane.

Standard solution 2: 10 μg/mL of retinyl palmitate from USP Retinyl Palmitate RS in n-Hexane.

System suitability solution: Mix equal volumes of Standard solution 1 and Standard solution 2.

Sample solution:

For Oral Liquid Preparation in single-unit containers, dilute the contents of NLT 10 single-unit containers, following the directions for use, as stated in the labeling. Weigh directly the individual contents delivered from each single-unit container, and calculate the average. [Note: Do not weigh the contents delivered by difference between full containers and empty containers. Capsules intended as single-unit containers are not rinsed after expulsion of the contents.] Mix the contents to obtain a homogeneous sample. Transfer an amount of the mixture to a suitable volumetric flask. Dissolve with methanol, and dilute with methanol quantitatively and stepwise, if necessary, to obtain a solution containing the equivalent of about 10 μg/mL of retinyl acetate, based on the labeled amount.

For Oral Liquid Preparation in multiple-unit containers: Dissolve an accurately measured volume of Oral Liquid Preparation in a suitable volume of n-Hexane, and dilute with n-Hexane quantitatively and stepwise, if necessary, to obtain a solution containing the equivalent of about 10 μg/mL of retinyl acetate, based on the labeled amount.

For Oral Liquid Preparation in aqueous vehicles: Transfer a weighed quantity, or an accurately measured volume of Oral Liquid Preparation, into a separatory funnel, and extract quantitatively with n-Hexane or other suitable solvent. Dilute with n-Hexane, quantitatively and stepwise, if necessary, to obtain a solution containing the equivalent of about 10 μg/mL of retinyl acetate, based on the labeled amount.

Chromatographic system

[See Chromatography (621), System Suitability].

Mode: LC

Detector: UV 325 nm

Column: 4.6 mm x 15 cm, packing L1

Flow rate: 1 mL/min

Injection volume: 40 μL

System suitability

Sample: System suitability solution

Suitability requirements

Resolution: NLT 10 between all-trans-retinyl acetate and all-trans-retinyl palmitate

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution 1 or Standard solution 2 and Sample solution.

Calculate the percentage of the labeled amount of vitamin A, as retinol (C₂₂H₃₀O), in each individual container:

Result = (p/A) x (CV) x (VL) / (U x 1000)

p = peak response of the corresponding all-trans-retinyl ester from the Sample solution.

A = peak response of the all-trans-retinyl ester from the appropriate Standard solution.

C = concentration of retinol (C₂₂H₃₀O) in the appropriate Standard solution (μg/mL).

W = weight or volume of Oral Liquid Preparation composite taken (mg or mL).

V = volume of the Sample solution (mL).

D = dilution factor (dilution volume/liters).

U = for multiple unit containers: labeled volume of each dosage unit (mL); or for single-unit containers: mass of contents (mg) of the contents obtained from each individual container, following the directions for use, as stated in this labeling.

T = labeled amount of vitamin A, as retinol (C₂₂H₃₀O), in each dosage unit (μg).

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2. Vitamin A

Acceptance criteria: \( 0.01 \text{ mg/mL} \leq C \leq 0.12 \text{ mg/mL} \)

**PERFORMANCE TESTS**
- **DELIVERABLE VOLUME (695):** Meets the requirements for Unit Liquid Preparation packaged in multiple-unit containers.
- **UNIFORMITY OF DOSAGE UNITS (905):**
  - Analysis: For Oral Liquid Preparation packaged in single-unit containers, empty the single-unit container, following the directions for use as stated in the labeling. [NOTE—Do not weigh the contents delivered by difference between full container and empty container.] Capsules intended for use as single-unit containers are not mixed after expiration of the contents.
  - Acceptance criteria: The contents as delivered, and weighed directly, meet the requirements.

**ADDITIONAL REQUIREMENTS**
- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. It may be packaged in single-unit containers. [NOTE—Capsules may be suitable as single-unit containers provided they are packaged in critical secondary containers as described in Good Packaging Practices (1773).]

**LABELING:** The label states that the product is Vitamin A Oral Liquid Preparation. Label the Oral Liquid Preparation to indicate the color in which the vitamin is present, and to indicate the amount of vitamin A delivered in each dosage unit in terms of the equivalent amount of retinol in mg/dosage unit. The amount of vitamin A delivered may also be stated in USP Units/dosage unit, on the basis that 1 USP Vitamin A Unit equals the biological activity of 0.33 mg of all-trans-retinol. Capsules used as single-unit containers may be exempt from the requirements of individual labeling, provided they are packaged in an appropriately labeled secondary container, including directions for use and delivery of each dosage unit. Oral Liquid Preparation, labeled as Oral Liquid Preparation packaged in multiple-unit containers to indicate the volume of each dosage unit.

**USP REFERENCE STANDARDS (11):**
- USP Retinyl Acetate RS
- USP Retinyl Palmitate RS
ANNEX 3

Nutrition International/United Nations Children's Fund product technical specifications

ANNEX B: Product Technical Specifications

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

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Product Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 1</td>
<td>200,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES</td>
<td>Opaque red, soft gelatin capsules with nipple. PMS 167c 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.</td>
</tr>
<tr>
<td></td>
<td>500 capsules per bottle</td>
<td>Desired Shelf-life: 36 months</td>
</tr>
<tr>
<td>Item 2</td>
<td>200,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES</td>
<td>Opaque red, soft gelatin capsules with nipple. PMS 167c 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.</td>
</tr>
<tr>
<td></td>
<td>100 capsules per bottle</td>
<td>Desired Shelf-life: 36 months</td>
</tr>
<tr>
<td>Item 3</td>
<td>100,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>500 capsules per bottle</td>
<td>Desired Shelf-life: 36 months</td>
</tr>
<tr>
<td>Item 4</td>
<td>Item: 100,000 IU VITAMIN A Oral Liquid Preparation (USP) or VITAMIN A Oral Solution (Ph. Int.) as SOFT GELATIN CAPSULES</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>100 capsules per bottle</td>
<td>Desired Shelf-life: 36 months</td>
</tr>
</tbody>
</table>

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These technical product specifications should not be modified without the permission of Nutrition International and the United Nations Children's Fund.
GENERAL PRODUCT TYPE & DESCRIPTION

FINISHED PRODUCT


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 worldwide. 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)1, 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 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 55.0% to NLT 50.0% 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 Bæreiss 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.


2.3. The secondary packaging for vitamin A soft gelatin capsules must comply with the current UNICEF Warehouse Packaging Technical Standards and Specifications.¹

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,² 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.

² 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.
³ 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 of 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 Pharmacopeial 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 999.

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:

<table>
<thead>
<tr>
<th>Storage</th>
<th>Testing parameters</th>
<th>Functionality</th>
<th>Level of microbial contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General appearance</td>
<td>Assay of capsule contents/ft</td>
<td>Uniformity of dosage units</td>
</tr>
<tr>
<td></td>
<td>Vit A of [%]</td>
<td>Soft gel caps</td>
<td>Vit A [IU]</td>
</tr>
<tr>
<td>Specifications</td>
<td>Pass/ fail</td>
<td>Pass/ fail</td>
<td>90.0-120.0% of labeled amount of vit. A</td>
</tr>
<tr>
<td>Initial*</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Accelerated</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>1 Month</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Long-term</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>9 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>12 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>18 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>24 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>36 Months</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Time point "0" (TPD), 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 TPD as described above.

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4. To be defined by refs to meet NUNICEF technical specification – Look for organoleptic properties such as leaking, clumping, melting, etc.
5. USP – VA CLP monograph (Assay VI. A). As per official correspondence with the USP, the Dietary Supplement Dosage Forms Subcommittee members have agreed to support the request to reduce the lower limit of vitamin A from NLT 95.0% to NLT 90.9% of labeled claim. This change was reflected in the April, 2013 publication of the USP Revision Bulletin.
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.