



**DRAFT MONOGRAPH FOR *THE INTERNATIONAL PHARMACOPOEIA***

**PAEDIATRIC RETINOL ORAL SOLUTION**

**(August 2010)**

***DRAFT FOR COMMENT***

This document was provided by a quality control expert and was discussed at the recent WHO tele-/videoconference on specifications for medicines and quality control laboratory issues held on 25 August 2010. Should you have any comments thereon, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mails: [kopps@who.int](mailto:kopps@who.int) with a copy to Dr Herbert Schmidt ([schmidth@who.int](mailto:schmidth@who.int)) by 10 October 2010.

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**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT**

**QAS/10.389**

***International Pharmacopoeia monograph on Paediatric retinol oral solution***

	<b>Date</b>
Preparation of first draft by laboratory	August 2010
Preliminary discussion of the first draft during the tele-/ videoconference on specifications for medicines and quality control laboratory issues	25 August 2010
Mailing of draft monograph for comments	September 2010
Collation of comments received	October 2010
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Any further action as required	...

**DRAFT MONOGRAPH FOR *THE INTERNATIONAL  
PHARMACOPOEIA***

**PAEDIATRIC RETINOL ORAL SOLUTION**

**(August 2010)**

**Other name.** Paediatric Vitamin A oral solution.

**Category.** Vitamin.

**Storage.** Paediatric retinol oral solution should be kept in a tight, light-resistant, container, protected from heat and light.

**Labelling.** The labelling should state the name of the retinol ester or esters present, the proportion of Vitamin A expressed in International Units (IU), and the names and proportions of any stabilizing agents added.

**Additional information.** Strength in the current WHO Model list of essential medicines for children: Oral oily solution: 100 000 IU (as palmitate)/ml in multidose dispenser.

**Requirements**

Complies with the monograph for [“Liquid preparation 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 antioxidants. The oral solution contains not less than 90% and not more than 120% of the amount of vitamin A stated on the label.

**Identity tests**

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

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 12 volumes of cyclohexane R and 1 volumes of ether R as the mobile phase. Apply separately to the plate 2 µl of each of 4 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 acetate RS equivalent to 5000 IU of vitamin A per ml. For solution (C) prepare a solution of retinol propionate RS equivalent to 5000 IU of vitamin A per ml. For solution (D) prepare a solution of retinol palmitate RS equivalent to 5000 IU of vitamin A per ml. 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 obtained with solution (A) corresponds in position and appearance to one or more of the spots obtained with solutions (B), (C), and (D).

- A.2. Carry out the test as described under [1.14.1 Thin-layer chromatography](#), using the conditions described above under test A.1 but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber, allow it to dry in air, and spray with antimony trichloride TS. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position and appearance to one or more of the spots obtained with solutions (B), (C), and (D).

- B. Dissolve a drop of the oral solution in about 1 ml of dichloromethane R and add 5 ml of antimony trichloride TS; a blue colour is immediately produced which turns gradually to violet-red.
- C. 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).
- D. 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.

**Assay.** Carry out the assay as rapidly as possible, avoiding exposure to actinic light and oxidizing agents, and maintaining whenever possible an atmosphere of nitrogen above the solution.

- Either method A, where valid, or B may be applied.
- A. Carry out each determination in duplicate. 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, measured against a solvent cell containing 2-propanol, lies between 325nm and 327nm. Measure the absorbances at 300nm, 326nm, 350nm, and 370 nm. Repeat the readings at each wavelength and take the mean values. Calculate the ratio  $A_{\lambda}/A_{326}$  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 International Units per millilitre from the expression:  $A_{326} \times V \times d \times 1900/100m$ , where  $A_{326}$  is the absorbance at 326 nm,  $V$  is the total volume used for the dilution to give 10-15 IU per ml,  $m$  is the mass of sample used in g,  $d$  is the density of the

oral solution in g/ml and 1900 is the factor to convert the specific absorbances of esters of retinol into IU per g.

If one or more of the ratios  $A_{\lambda}/A_{326}$  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 x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with octadecysilyl groups (5  $\mu$ m). 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 tetrabutylammonium hydroxide TS in 2-propanol R. Swirl gently and let the mixture react for 10 minutes at 60-65°C for hydrolysis, swirling occasionally. Allow to cool to room temperature, dilute to volume with 2-propanol R containing 1 g/l butylated hydroxytoluene R, and homogenise 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 or retinol palmitate 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 10  $\mu$ l of solution (2) in six replicate injections into the chromatographic system. The assay is not valid unless the relative standard deviation for the peak area of retinol is less than 2.0%.

Inject alternatively 10  $\mu$ l each 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) and calculate the content of vitamin A.

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