Monograph for Sodium phosphate (\(^{32}\)P) injection (Natrii phosphatis (\(^{32}\)P) injectio) (January 2018)

DRAFT FOR COMMENT

Please send any comments on the revision of this draft document to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int) with a copy to Mrs Xenia Finnerty (finnertyk@who.int) by 16 March 2018.

Our working documents will be sent out electronically only and will also be placed on the Medicines website for comment under “Current projects”. If you do not already receive our draft working documents please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.

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Please send any request for permission to:

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### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/18.748

**Monograph for Sodium phosphate ($^{32}$P) injection**  
(Natrii phosphatis ($^{32}$P) injectio)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
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<tbody>
<tr>
<td>IAEA consultation</td>
<td>3–7 December 2012</td>
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<tr>
<td>IAEA consultation</td>
<td>6–10 May 2013</td>
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<tr>
<td>Draft monograph received from IAEA in track-change mode according to format/template described in QAS/13.544</td>
<td>June 2013</td>
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<tr>
<td>Discussion at informal consultation on new medicines, quality control and laboratory standards</td>
<td>12–14 June 2013</td>
</tr>
<tr>
<td>Feedback to IAEA by WHO Secretariat</td>
<td>June 2013</td>
</tr>
<tr>
<td>Circulation for comments to IAEA and WHO Panel of Experts</td>
<td>June 2013</td>
</tr>
<tr>
<td>Feedback to IAEA, as appropriate</td>
<td>August–September 2013</td>
</tr>
<tr>
<td>Discussion during WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)</td>
<td>October 2013</td>
</tr>
<tr>
<td>Follow up by IAEA, including review of comments received</td>
<td>October 2013–February 2014</td>
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<tr>
<td>Discussion of revised version at IAEA consultation, Vienna, Austria</td>
<td>February 2014</td>
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<tr>
<td>Finalization by IAEA</td>
<td>February 2014</td>
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<tr>
<td>Circulation of revision to WHO and IAEA mailing list of experts for comments</td>
<td>March 2014</td>
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<tr>
<td>Compilation of feedback</td>
<td>April 2014</td>
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<tr>
<td>Discussion at informal consultation on Specifications for The International Pharmacopoeia and laboratory standards in Geneva</td>
<td>3–4 April 2014</td>
</tr>
<tr>
<td>Event Description</td>
<td>Date/Time</td>
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<td>Compilation of feedback to IAEA</td>
<td>May 2014</td>
</tr>
<tr>
<td>Presentation to forty-ninth WHO ECSPP</td>
<td>13–17 October 2014</td>
</tr>
<tr>
<td>Update during the fiftieth WHO ECSPP</td>
<td>12–16 October 2015</td>
</tr>
<tr>
<td>Review and discussion of situation regarding monograph development for radiopharmaceuticals at informal consultation on quality control laboratory tools and specifications for medicines</td>
<td>9–11 May 2016</td>
</tr>
<tr>
<td>IAEA update during the fifty-first WHO ECSPP</td>
<td>17–21 October 2016</td>
</tr>
<tr>
<td>Review and discussion during informal consultation on quality control laboratory tools and specifications for medicines</td>
<td>2–4 May 2017</td>
</tr>
<tr>
<td>IAEA delegated final review and modifications to Professor Alain Nicolas, France</td>
<td>May–January 2018</td>
</tr>
<tr>
<td>Mailing of revised monograph for public consultation</td>
<td>January 2018</td>
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<tr>
<td>Following recommendation by the 52nd WHO ECSPP finalization of the monograph text, in accordance with the procedure, for publication in the 8th edition of The International Pharmacopoeia (2018), provided no major issues arise</td>
<td>March–April 2018</td>
</tr>
<tr>
<td>Presentation to the fifty-third ECSPP</td>
<td>22–26 October 2018</td>
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<td>Any further action as necessary</td>
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Monograph for Sodium phosphate \(^{32}\text{P}\) injection (\text{Natrii phosphatis \(^{32}\text{P}\) injectio})

**Latin.** Natrii phosphatis \(^{32}\text{P}\) injectio

**English.** Sodium phosphate \(^{32}\text{P}\) injection

**Structural formula**

\[
\begin{align*}
\text{Sodium dihydrogen \[^{32}\text{P}\]phosphate} & \quad & \text{Disodium hydrogen \[^{32}\text{P}\]phosphate} \\
\begin{array}{c}
\text{Na}^+ \quad \overset{\text{O}}{\text{O}} \quad \overset{\text{OH}}{\text{OH}} \\
\end{array} & \quad & \begin{array}{c}
\text{Na}^+ \quad \overset{\text{O}}{\text{O}} \quad \overset{\text{OH}}{\text{OH}} \quad + \text{Na} \\
\end{array}
\end{align*}
\]

**Molecular formula.** \(\text{H}_2\text{NaO}_4\text{P}^{32}\text{P}\) and \(\text{HNa}_2\text{O}_4\text{P}^{32}\text{P}\)

**Relative molecular mass.** For \(\text{H}_2\text{NaO}_4\text{P}^{32}\text{P}\) is 121.006, and for \(\text{HNa}_2\text{O}_4\text{P}^{32}\text{P}\) is 142.998

**Chemical name.** Mixture of sodium dihydrogen \([^{32}\text{P}]\)phosphate and disodium hydrogen \([^{32}\text{P}]\)phosphate

**Other names.** Sodium phosphate-P32, Sodium orthophosphate-32P, Phosphotope

**Description.** Sodium phosphate \(^{32}\text{P}\) injection is a clear, colourless solution. Phosphorus-32 has a half-life of 14.3 days.

**Category.** Therapeutic.

**Storage.** Sodium phosphate \(^{32}\text{P}\) injection is kept in single-dose or multiple-dose containers at controlled room temperature (15–25 °C).

**Labelling.** The label complies with the General monograph of Radiopharmaceuticals. State the date of withdrawal of the first dose for multidose containers.

**Manufacture**

Phosphorus-32 may be produced by neutron irradiation of sulphur.

The injection may be sterilized by "Heating in an autoclave" (see 5.8 Methods of sterilization).
Additional information

Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in millilitres.

It is advised to use acrylic sheet for radiation protection and not lead.

Requirements

Complies with the monograph for Parenteral Preparations and with that for Radiopharmaceuticals.

Definition

Sodium phosphate ($^{32}$P) injection is a sterile solution of disodium and monosodium ($^{32}$P) orthophosphates, suitable for intravenous administration and that contains sufficient sodium chloride to make the solution isotonic. The injection contains not less than 90% and not more than 110% of the content of phosphorus-32 stated on the label at the reference date and time.

Not less than 95% of the total radioactivity corresponds to phosphorus-32 in the form of orthophosphate ion. The specific activity is not less than 11.1 MBq of phosphorus-32 per mg of phosphate ion at the reference date and time stated on the label.

Identity tests

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

A. Record the beta-ray spectrum using a suitable instrument with a sample of phosphorus-32, suitably diluted if needed. The spectrum is concordant with the reference spectrum of a specimen of phosphorus-32 in that it exhibits a maximum energy at 1.71 MeV

Standardized phosphorus-32 solutions are available from laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 13.5 and 15 days.

C. In the test for Radiochemical purity, the chromatogram obtained contributes to the identification of the sodium phosphate ($^{32}$P). The activity in the ($^{32}$P) orthophosphate zone should not less than 95% of the total activity.

Ph

Perform the test as described under R1.5 or 1.13 Determination of pH under the monograph for Radiopharmaceuticals. The pH of the injection should be between 6.0 and 8.0.
Chemical purity

Total phosphate: maximum 89 µg/MBq.

The test solution is prepared by diluting the injection to be examined with water R to give a radioactivity concentration of 370 kBq of phosphorus-32 per mL. In a volumetric flask mix with shaking 1.0 mL of this solution with a mixture of 0.5 mL of ammonium molybdate solution R (100 g/L), 0.5 mL of 2.5 g/L solution of ammonium vanadate R and 1 mL of perchloric acid R and dilute to 5.0 mL with water R, mixing after each addition, and allow to stand for 30 minutes. Prepare the reference solution at the same time and in the same manner as the test solution using 1.0 mL of a solution containing 33 mg of orthophosphate ion per litre.

The spectrophotometer is set for measurement at 460 nm. Measure the absorbance of the test solution and the reference. The absorbance of the test solution is not more than the absorbance of the reference solution.

Sterility. Test for sterility will be initiated on the day of manufacture. The injection may be released for use before completion of the test. The injection complies with 3.2 Test for sterility, modified as described in the monograph for Radiopharmaceuticals.

Bacterial endotoxins

Perform the test as described under 3.4 Test for bacterial endotoxins, modified as described in the monograph for Radiopharmaceuticals. The injection contains not more than 175/V I.U of endotoxins per millilitre.

Radionuclidic purity

- Beta-ray spectrometry. Record the beta-ray spectrum using a suitable instrument and measure the half-life using a suitable method. The spectrum obtained with the preparation to be examined does not differ significantly from that obtained under the same conditions with a standardized phosphorus-32 solution.

- Gamma-ray spectrometry. No gamma-emitting radionuclides should be present when checked by gamma spectrometry.

Radiochemical purity

Perform the test as described under 1.14.2 Paper chromatography and ascending conditions using cellulose paper Whatman No 1 strips (30 x 330 mm). A mixture of 75 volumes of 2-propanol R, 10 volumes of 50% of trichloroacetic acid R, 14.4 volumes of distilled water and 0.6 volume of 10% ammonia solution is used as the mobile phase. The injection to be examined, suitably diluted with distilled water R to give an activity about 20000 counts per minute per 10 µL. Apply to the paper about 10 µL of the injection to be examined about 3 cm from one end of the strip. Develop the chromatogram (takes about 18 hours) till the solvent front reaches 27 cm from the point of the spotting. Allow the strip to air dry. Scan the strip using a
radiochromatogram scanner or cut into one cm sections and count using a suitable calibrated
counter. The $R_f$ values of metaphosphate, pyrophosphate and orthophosphate are 0.0, 0.4 and
0.6–0.8, respectively.

Calculate the percent. of $^{32}$P present as orthophosphate as follows:

$$\text{(percent.) Radiochemical purity} = \frac{\text{Activity in } ^{32}\text{P orthophosphate zone}}{\text{Total activity}} \times 100$$

The activity in the ($^{32}$P) orthophosphate zone should not less than 95% of the total activity.

**Radioactivity**

Measure the radioactivity using a suitable calibrated counting instrument as described under

*R.1.1 Detection and measurement of radioactivity.*