EAG/Panel/Working Party	Medicinal Chemicals 1
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Deadline for Comment	30 September 2017
Target Publication Date (subject to change)	**BP 2019**
Notes: Editorial change: The globule size text has been revised.	

Propofol Injection

Propofol Preparations

Action and use
Intravenous general anaesthetic.

DEFINITION

Propofol Injection is a sterile emulsion of Propofol in a suitable basis.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of propofol, $C_{12}H_{18}O$
95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a volume of the injection containing 0.1 g of Propofol with three 25-mL quantities of *hexane* and filter the combined extracts using a glass fibre filter (Whatman GF/C is suitable). Extract the filtrate with two 20-mL quantities of *methanol* (90%) and evaporate the combined extracts under reduced pressure. Dissolve the residue obtained in 2 mL of *absolute ethanol* and evaporate to dryness under reduced pressure. Dry the residue at 50° over *phosphorus pentoxide* for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Propofol (*RS 416*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity
pH, 6.0 to 8.5, Appendix V L.

Propofol quinone and propofol dimer
Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the well shaken injection with *propan-2-ol* to produce a solution containing 0.08% w/v of Propofol.

(2) 0.0008% w/v of *propofol BPCRS*, 0.00008% w/v of *propofol impurity J BPCRS* and 0.0002% w/v of *propofol dimer BPCRS* in *propan-2-ol* containing 6.8% v/v of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for at least three times the retention time of the principal peak.

MOBILE PHASE

40 volumes of *tetrahydrofuran* and 60 volumes of *water*.

When the chromatograms are recorded using the prescribed conditions the retention time of propofol is about 7 minutes. The retention times relative to the propofol are: propofol impurity J, about 0.8, propofol dimer about 2.5.

SYSTEM SUITABILITY

The test is not valid unless the *resolution* between the peaks due to propofol and propofol impurity J is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the areas of any peaks corresponding to propofol quinone (propofol impurity J) and propofol dimer are not greater than the areas of the corresponding peaks in the chromatogram obtained with solution (2) (0.1% and 0.25% respectively).

Globule size
Not more than 5000 globules greater than or equal to 2 µm per mL of a 0.01% v/v dilution in a filtered 0.9% w/v solution of sodium chloride using suitable equipment (possible techniques listed in the Appendix XIII A, or a Coulter counter is suitable). Repeat the procedure using the 0.9% w/v solution of *sodium chloride* only to determine the background count.

Free fatty acid
Not greater than 7 millimoles per litre, when determined by the following method. To 5 mL of a well shaken injection add 25 mL of a mixture of 40 volumes of *propan-2-ol*, 10 volumes of *n-heptane* and 1 volume of 0.5M *sulfuric acid* and shake for 1 minute. Allow to stand for 10 minutes, add 15 mL of *n-heptane* and 15 mL of *water*. Mix by inverting the container 10 times and allow to stand for 15 minutes. To 15 mL of the upper phase add 5 mL of *aqueous nile blue A solution* and pass a stream of *nitrogen*, previously passed through 0.1M *sodium hydroxide*, through the solution. Titrate with 0.02M *sodium hydroxide VS*, using a microburette. Calculate the content of free fatty acid from a calibration curve prepared from quantities of 1, 2, 4, 6 and 8 mL of a 1.282% w/v solution of *palmitic acid* in n-*heptane*, each diluted to 50 mL with n-*heptane*. Carry out the method described above, using 5 mL of each solution and beginning at the words 'add 25 mL of a mixture…'.

Lysolecithin
Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of well shaken injection with mobile phase to produce a solution containing 0.1% w/v of Propofol and filter through a 0.45-µm nylon filter.

(2) 0.01% w/v of *lysolecithin* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 250 µL of each solution.

MOBILE PHASE

7 volumes of *orthophosphoric acid*, 200 volumes of *water* and 300 volumes of *acetonitrile.*

LIMITS

Not greater than 0.2% w/v, calculated using the following expression:

$$\frac{A_1 \times C_2 \times f}{A_2}$$

where:

A_1	=	peak area of lysolecithin in solution (1)
A_2	=	peak area of lysolecithin in solution (2)
C_2	=	concentration of lysolecithin in solution (2)
f	=	dilution factor used for solution (1)

Bacterial endotoxins
Carry out the test for *Bacterial endotoxins*, Appendix XIV C. Dilute the injection in *water BET* to give an emulsion containing 5 mg per mL (solution A). The endotoxin limit concentration of solution A is 1.65 IU endotoxin per mL.

ASSAY
Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the well shaken injection with *propan-2-ol* to produce a solution containing 0.08% w/v of Propofol.

(2) 0.08% w/v of *propofol BPCRS* in *propan-2-ol* containing 6.8% v/v of *water*.

(3) 0.0008% w/v of *propofol BPCRS* and 0.00008% w/v of *propofol impurity J BPCRS* in *propan-2-ol* containing 6.8% v/v of *water.*

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Propofol quinone and propofol dimer may be carried out but using a detection wavelength of 275 nm.

SYSTEM SUITABILITY

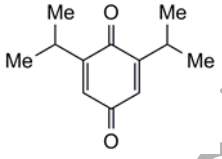
The test is not valid unless the *resolution* between the peaks due to propofol and propofol impurity J is at least 2.5.

DETERMINATION OF CONTENT

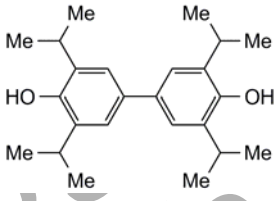
Calculate the content of $C_{12}H_{18}O$ in the injection from the chromatograms obtained and using the declared content of $C_{12}H_{18}O$ in *propofol BPCRS.*

STORAGE
Propofol Injection should be stored at a temperature not exceeding 25°. It should not be allowed to freeze.

IMPURITIES
The impurities limited by the requirements of this monograph include:



A. 2,6-bis(1-methylethyl)-1,4-benzoquinone (propofol quinone) (Ph. Eur. impurity J)



B. 3,3',5,5'-tetrakis(1-methylethyl)biphenyl-4,4'-diol (propofol dimer)