15 min, and shake by mechanical means until all the solid is dispersed (usually 20 min). Allow the solution to cool to room temperature, and dilute with water to volume. Pass a portion of this solution through a PTFE (or equivalent) filter of 0.45-µm pore size, and discard the first 5 mL of filtrate.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for primidone related compound A and primidone are 0.5 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 4.0 between primidone related compound A and primidone, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Primidone RS in the *Standard solution* (µg/mL)
C_U = concentration of primidone in the *Sample solution* (µg/mL)
F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

[NOTE—Disregard impurity peaks that are less than •0.05%.•(RB 1-Nov-2011)]

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Primidone related compound A[a]	0.5	0.76	0.1
Primidone	1.0	—	—
Phenobarbital	1.6	1.4	0.1
Primidone related compound C[b]	1.9	0.92	0.1
•2-Cyano-2-phenylbutyramide[c]	2.2	—	—•(RB 1-Nov-2011)
2-Phenylbutyric acid	4.1	0.91	0.1
•Phenylpropyl-primidone[c]	11.4	—	—•(RB 1-Nov-2011)
Any individual unspecified degradation product	—	1.0	0.1
Total impurities	—	—	•0.5•(RB 1-Nov-2011)

[a] 2-Ethyl-2-phenylmalonamide.
[b] 2-Phenylbutyramide.
•[c] Process impurities controlled in the drug substance. Included for identification purposes only. Not reported for the drug product and not included in *Total impurities*.•(RB 1-Nov-2011)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.
- **LABELING:** Tablets intended solely for veterinary use are so labeled.

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Primidone RS
  USP Primidone Related Compound A RS
  2-Ethyl-2-phenylmalonamide.
  $C_{11}H_{14}N_2O_2$ 206.24

Propofol Injectable Emulsion

DEFINITION

Propofol Injectable Emulsion contains Propofol in a 10% (w/v) oil-in-water sterile emulsion. The aqueous component contains glycerol, a suitable antimicrobial agent, and Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of propofol ($C_{12}H_{18}O$). It contains a suitable emulsifying agent.

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION** ⟨197U⟩
  Wavelength range: 200–450 nm
  Standard solution: 100 µg/mL
  Sample solution: Dilute a volume of Injectable Emulsion, equivalent to 10 mg of propofol, with isopropyl alcohol to 100 mL.
  Medium: Isopropyl alcohol
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**
  Diluent: Dilute 68 mL of water with isopropyl alcohol to 1 L.
  Mobile phase: Tetrahydrofuran and water (4:6)
  Standard solution: 0.8 mg/mL of USP Propofol RS in *Diluent*
  Sample solution: Transfer a volume of well-shaken Injectable Emulsion, equivalent to about 40 mg of propofol, to a 50-mL volumetric flask. Dissolve in and dilute with isopropyl alcohol to volume, and mix. The solution contains about 0.8 mg/mL of propofol.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 275 nm
  Column: 5-mm × 10-cm; 5-µm packing L1
  Flow rate: 2 mL/min
  Injection size: 20 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Column efficiency: NLT 1000 theoretical plates
  Tailing factor: NMT 1.5
  Relative standard deviation: NMT 2%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of propofol ($C_{12}H_{18}O$) in the portion of Injectable Emulsion taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Propofol RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of propofol in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

- **LIMIT OF FREE FATTY ACIDS**

[NOTE—To obtain a titer of sufficient sensitivity for the blank reagent, it is necessary to add stearic acid at a concentration of approximately 1.0 mMol/L.]

Blank titration: Weigh about 142.3 mg of stearic acid into a 500-mL volumetric flask. Dissolve in and dilute with dehydrated alcohol to volume to obtain the blank solution. Pipet 10 mL of the blank solution into a 100-mL beaker, and proceed as directed under *Analysis*, beginning with "add 0.5 mL of 0.05 N hydrochloric acid".

Calculate the blank correction, *B*, in mMol/L:

$$\text{Result} = (NV_{TB}/V_B) - N_{SA}$$

N = concentration of the titrant (mMol/L)
V_{TB} = volume of the titrant added between the first and second inflection points for the blank titration (mL)
V_B = volume of the blank solution used for the analysis (mL)
N_{SA} = concentration of stearic acid (mMol/L)

Analysis

Sample: A volume of Injectable Emulsion, nominally equivalent to 100 mg of propofol

Transfer the *Sample* to a 100-mL beaker. Add 0.5 mL of 0.05 N hydrochloric acid, then dilute with a solution of alcohol and water (45:20) to 60 mL. Titrate with 0.05 M sodium hydroxide VS to a potentiometric endpoint, using a suitable electrode.

Calculate the free fatty acid content, in mMol/L:

$$\text{Result} = (NV_T/V_S) - B$$

N = concentration of the titrant (mMol/L)
V_T = volume of the titrant added between the first and second inflection points (mL)
V_S = volume of Injectable Emulsion used for the analysis (mL)
B = blank correction factor (mMol/L), calculated as shown above

Acceptance criteria: NMT 5 mMol/L

Change to read:

- **ORGANIC IMPURITIES**

Mobile phase, Diluent, and **Sample solution:** Prepare as directed in the *Assay*.

•**System suitability solution:**• (IRA 1-Nov-2011) Dissolve quantities of USP Propofol RS, USP Propofol Related Compound A RS, and USP Propofol Related Compound B RS in *Diluent* to obtain a solution having concentrations of 0.8 mg/mL of propofol and 0.002 and 0.0008 mg/mL of propofol related compound A and propofol related compound B, respectively.

•**Standard solution:** 0.002 mg/mL of USP Propofol Related Compound A RS and 0.0008 mg/mL of USP Propofol Related Compound B RS in *Diluent*• (IRA 1-Nov-2011)

Chromatographic system: Proceed as directed in the *Assay*, except that detection is at 254 nm.

System suitability

Sample: •*System suitability solution*• (IRA 1-Nov-2011)

[NOTE—The relative retention times for propofol related compound B, propofol, and propofol related compound A are about 0.8, 1.0, and 2.5, respectively.]

Suitability requirements

Resolution: NLT 2.5 between propofol and propofol related compound B

Column efficiency: NLT 1000 theoretical plates based on the propofol peak

Tailing factor: NMT 1.5 for the propofol peak

Relative standard deviation: NMT 2% for the propofol peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the content of propofol related compound A and propofol related compound B, as a percentage of the label content of propofol, in the portion of Injectable Emulsion taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of propofol related compound A or propofol related compound B from the *Sample solution*
r_S = peak response of propofol related compound A or propofol related compound B from the *Standard solution*
C_S = concentration of USP Propofol Related Compound A RS or USP Propofol Related Compound B RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of propofol in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.5% of propofol related compound A; NMT 0.5% of propofol related compound B

SPECIFIC TESTS

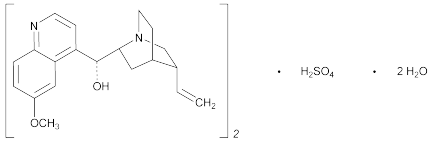
- **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** It contains NMT 0.33 USP Endotoxin Unit/mg of propofol.
- **STERILITY TESTS ⟨71⟩:** Meets the requirements
- **pH ⟨791⟩:** 4.5–8.5
- **GLOBULE SIZE DISTRIBUTION IN LIPID INJECTABLE EMULSIONS ⟨729⟩:** Meets the requirements
- **OTHER REQUIREMENTS:** It meets the requirements under *Injections* ⟨1⟩.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve under an inert atmosphere of nitrogen. Store at controlled room temperature. Do not freeze.
- **LABELING:** Label it to include the following: Shake well before use. Do not use if there is evidence of excessive creaming or aggregation, if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised. Slight creaming, which should disappear after shaking, may be visible upon prolonged standing.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Endotoxin RS
USP Propofol RS
USP Propofol Related Compound A RS
3,3′-5,5′-Tetraisopropyldiphenol.
USP Propofol Related Compound B RS
2,6-Diisopropylbenzoquinone.

Quinine Sulfate



$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ 782.94

Cinchonan-9-ol, 6′-methoxy-, (8α,9*R*)-, sulfate (2:1) (salt), dihydrate;
Quinine sulfate (2:1) (salt) dihydrate [6119-70-6].

Anhydrous 746.93
[804-63-7].