Bagian : QC

Due date : 7-Apr-26

Tanggal : 12-Jan-26

ANALISA PERMINTAAN BARANG

No	Kode Barang	Nama Barang	Satuan	Stok Saat Ini (A)	Rencana Kebutuhan (B)	Kekurangan (A -B + C)	Pending Penerimaan (C)	Jumlah	Realisasi Pembelian	Realisasi Penggunaan
1	IBS00170	RS Isoflurane	ml	0	2	-2	0	2	0	0
2	IBS00173	RS Sevoflurane	ml	0	2	-2	0	2	0	0

Catatan :

1. RS Isoflurane (1 Ampul @ 1 ml) catalog no : 1349003 Ex. USP

- Digunakan sebagai pembuatan standar IR dan WS Isoflurane untuk analisa bahan baku, produk jadi dan stabilita produk isoflurane '
- Estimasi harga : $259.00/ampul
- Pemesanan pertama kali untuk kebutuhan dept QC

2. RS Sevoflurane (1 Ampul @1 ml) catalog no : 1612540 Ex. USP

- Digunakan sebagai pembuat standar IR dan WS Sevoflurane untuk analisa bahan baku, produk jadi, dan stabilita produk Sevoflurane
- Estimasi harga : $302.00/ampul
- Pemesanan pertama kali untuk kebutuhan dept QC

Latar belakang permintaan:

- Untuk memenuhi kebutuhan pembuatan working standar (WS) yang nantinya akan digunakan untuk analisa produk antara, ruahan, produk jadi, Valpro, Stabilita produk dan bahan baku.
- Saat ini belum pernah dilakukan pembelian Reference Standars tersebut.
- Terlampir latar belakang pemesanan, penawaran harga,USP terkini dan Rencana kebutuhan.

Pemohon

12/26 SOS 01

.....

Mengetahui

13/01/26

.....

mersi PT. MERSIFARMA TM SUKABUMI-INDONESIA	**FORMULIR LATAR BELAKANG PERMINTAAN BARANG HABIS PAKAI** **DEPARTEMEN:** QUALITY CONTROL	*Diisi oleh Pemohon* No. : 008 /LBPBHP/ I /2026

Nama Barang Habis Pakai:
Baku Pembanding Isoflurane
Catalog No: 1349003
Berlaku untuk satu jenis barang

18500170

Rencana Waktu Penggunaan:
7 April 2026

Lead time Purchasing:
90 hari

Masa Waktu Pakai 1 tahun

Masa Frekuensi Pakai Setiap kali pembakuan WS Isoflurane

☑ Permintaan Item Baru

☐ Permintaan Kebutuhan Jadwal Kerja

☐ Bahan Penunjang	☐ Perlengkapan Listrik	☐ Innovator	☐ Kalibrasi
☐ Suku Cadang	☐ Alat Tulis	☐ Sample Bahan Kemas	☐ Perbaikan
☐ Bahan Kebersihan	☐ Hadware	☐ Sample Bahan Baku	☐ Marketing Promosi
☐ Inkjet/Laserjet Print	☐ _____	☐ Kualifikasi	☐ _____

SYARAT WAJIB PERMINTAAN BARU
1. Sertakan Foto Barang Baru.
2. Dibuat hanya sekali untuk awal mendaftarkan ke sistem QAD.
3. Pemesanan selanjutnya menggunakan Analisa Permintaan Barang dengan melampirkan hasil verifikasi stok fisik (kartu stok/bin card).

SYARAT WAJIB PERMINTAAN JADWAL KERJA
1. Formulir Perbaikan (jika dibutuhkan).
2. Setiap pengajuan menyertakan jadwal/timetable.
3. Dibuat setiap mengajukan kebutuhan untuk memenuhi rencana jadwal kerja, sekalipun barang sudah terdaftar di sistem QAD.

Digunakan untuk	Pembuatan standar IR dan WS Isoflurane untuk analisa bahan baku, produk jadi dan stabilita produk Isoflurane. Beli 2 vial
Latar belakang permintaan	1. Untuk memenuhi kebutuhan pembuatan Working Standard (WS) Isoflurane yang nantinya WS akan digunakan untuk analisa produk antara, ruahan, produk jadi, valpro, stabilita produk dan bahan baku Isoflurane 2. Saat ini belum pernah dilakukan pembelian RS Isoflurane

☐ Perlu Minimum Stock
Tentukan Reorder Point

Dibuat:	Diperiksa:	Menyetujui:
VERONICA B.D	RGT.	
Tgl. 07/01/26	Tgl. 07/01/26.	Tgl. 07/01/26
(Staf/Koord.)	*(Koord./Spv/Ast. Mgr)*	*(Kepala Departemen)*

Nomor Dokumen	: COM-FPT/001A.00	Tanggal Berlaku	: 11 SEP 2023	Disetujui oleh	:

mersi
PT. MERSIFARMA TM
SUKABUMI-INDONESIA

FORMULIR LATAR BELAKANG PERMINTAAN BARANG HABIS PAKAI

DEPARTEMEN: QUALITY CONTROL

Diisi oleh Pemohon

No. : 009 /LBPBHP/ I /20 26

Nama Barang Habis Pakai:

Baku Pembanding Sevoflurane
Catalog No: 1612540

Berlaku untuk satu jenis barang

10S00173

Rencana Waktu Penggunaan:
7 April 2026

Lead time Purchasing:
90 hari

Masa Waktu Pakai 1 tahun

Masa Frekuensi Pakai Setiap kali pembakuan WS Sevoflurane

☑ Permintaan Item Baru

☐ Permintaan Kebutuhan Jadwal Kerja

☐ Bahan Penunjang	☐ Perlengkapan Listrik	☐ Innovator	☐ Kalibrasi
☐ Suku Cadang	☐ Alat Tulis	☐ Sample Bahan Kemas	☐ Perbaikan
☐ Bahan Kebersihan	☐ Hadware	☐ Sample Bahan Baku	☐ Marketing Promosi
☐ Inkjet/Laserjet Print	☐ _____	☐ Kualifikasi	☐ _____

SYARAT WAJIB PERMINTAAN BARU
1. Sertakan Foto Barang Baru.
2. Dibuat hanya sekali untuk awal mendaftarkan ke sistem QAD.
3. Pemesanan selanjutnya menggunakan Analisa Permintaan Barang dengan melampirkan hasil verifikasi stok fisik (kartu stok/bin card).

SYARAT WAJIB PERMINTAAN JADWAL KERJA
1. Formulir Perbaikan (jika dibutuhkan).
2. Setiap pengajuan menyertakan jadwal/timetable.
3. Dibuat setiap mengajukan kebutuhan untuk memenuhi rencana jadwal kerja, sekalipun barang sudah terdaftar di sistem QAD.

Digunakan untuk	Pembuatan standar IR dan WS Sevoflurane untuk analisa bahan baku, produk jadi dan stabilita produk Sevoflurane. Beli 2 vial
Latar belakang permintaan	1. Untuk memenuhi kebutuhan pembuatan Working Standard (WS) Sevoflurane yang nantinya WS akan digunakan untuk analisa produk antara, ruahan, produk jadi, valpro, stabilita produk dan bahan baku Sevoflurane 2. Saat ini belum pernah dilakukan pembelian RS Sevoflurane

☐ Perlu Minimum Stock
Tentukan Reorder Point

Dibuat:	Diperiksa:	Menyetujui:
VABIOLA	Oktori Scorpio.	
Tgl. 07/01 26	Tgl. 07/01 26	Tgl. 07/01/26
(Staf/Koord.)	*(Koord./Spv/Ast. Mgr)*	*(Kepala Departemen)*

Nomor Dokumen	: COM-FPT/001A.00	Tanggal Berlaku	: 11 SEP 2023	Disetujui oleh	:

Last Updated On: December 3, 2025

USP Catalog

Catalog #	Status	Product Name	Product Type	Current Lot	Previous Lot (VUD)	CAS #	NDC #	Unit Price	Co. Of Origin	Material Origin	UN #	Net Weight	Unit Of Measure	Commodity Codes (HS Codes)*	Special Restriction	Pkg. Type	USMCA Eligible	KORUS Eligible	Base Control Drug	Base Control Drug %	Subcategory
																					Medicines
1348543	Active	Isoeugenyl Acetate (150 mg)	Reference Standard	F144M0		93-29-8	N/A	$323.00	CN	Chemical Synthesis		150	mg	2915399500		VIAL	No	No			Botanicals-Herbal Medicines
1348601	Active	Red Clover Aerial Parts Isoflavone Aglycones Dry Extract (500 mg)	Reference Standard	F049R0		N/A	N/A	$137.00	CH	Plant		500	mg	1302190200		VIAL	No	No			Botanicals-Herbal Medicines
1348907	Active	Isoflupredone Acetate (200 mg)	Reference Standard	R10880	F0C109 (30-SEP-2020)	338-98-7	N/A	$302.00	IN	Chemical Synthesis		200	mg	2937220000		VIAL	No	No			Steroids
1349003	Active	Isoflurane (1 mL)	Reference Standard	R151S0	R064L0 (30-JUN-2022)	26675-46-7	N/A	$259.00	US	Chemical Synthesis	UN3334	1	mL	2909191800		AMPULE	No	No			Anaesthetics
1349014	Active	Isoflurane Related Compound A (0.1 mL) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether)	Reference Standard	R219U0	R14980 (31-JUL-2026)	32778-08-8	N/A	$991.00	IN	Chemical Synthesis	UN3334	0.1	mL	2909191800		AMPULE	No	No			Anaesthetics
1349025	Active	Isoflurane Related Compound B (0.1 mL) (2,2,2-Trifluoroethyl difluoromethyl ether)	Reference Standard	R15800	R126U0 (31-MAR-2023)	1885-48-9	N/A	$996.00	US	Chemical Synthesis	UN3334	0.1	mL	2909191800		AMPULE	No	No			Anaesthetics
1349149	Active	Isoguaifenesin (30 mg)	Reference Standard	F130Q0		14007-09-1	N/A	$448.00	AU	Chemical Synthesis		30	mg	2909490000		VIAL	No	No			Cough and Cold
1349502	Active	L-Isoleucine (200 mg)	Reference Standard	R14150	R049B0 (30-JUN-2022)	73-32-5	N/A	$277.00	BR	Fermentation - Microbial		200	mg	2922498050		VIAL	No	No			Amino Acids
1349604	Active	Isomalathion (50 mg) (Diethyl 2-{[methoxy(methylthio)phosphoryl]thio}succinate)	Reference Standard	R188P0	G0D311 (31-OCT-2021)	3344-12-5	N/A	$814.00	IN	Chemical Synthesis	UN3018	50	mg	2930909275		AMPULE	No	No			Antimicrobials
1349626	Active	Isomalt (200 mg)	Reference Standard	R05510	R01880 (31-MAR-2019)	64519-82-0	N/A	$305.00	DE	Plant		200	mg	2940006000		VIAL	No	No			Binders & Fillers
1349637	Active	Isomaltulose (5 g)	Reference Standard	R167E0	F0I340 (31-MAR-2023)	58024-13-8	N/A	$265.00	DE	Plant		5	g	2940006000		BOTTLE	No	No			Sweeteners
1349659	Active	Isometheptene Mucate (200 mg)	Reference Standard	R09770	G0F338 (31-DEC-2019)	7492-31-1	N/A	$346.00	CA	Chemical Synthesis		200	mg	2921196195		VIAL	No	No			Analgesics
1349670	Active	Isonaringin (30 mg) ((RS)-5-Hydroxy-2-(4-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-chromen-7-yl 6-O-	Reference Standard	R136R0	F041R0 (30-APR-2022)	14259-46-2	N/A	$656.00	CN	Plant		30	mg	2938100000		VIAL	No	No			Botanicals-Herbal Medicines

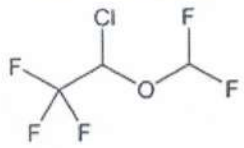
07/20

USP Catalog

Catalog #	Status	Product Name	Product Type	Current Lot	Previous Lot (VUD)	CAS #	NDC #	Unit Price	Co. Of Origin	Material Origin	UN #	Net Weight	Unit Of Measure	Commodity Codes (HS Codes)*	Special Restriction	Pkg. Type	USMCA Eligible	KORUS Eligible	Base Control Drug	Base Control Drug %	Subcategory
																					ents
1612415	Active	Sesame Oil Related Compound A (12 mg/vial; 2 vials) (1,2-dilinoleoyl-3-oleoyl-rac-glycerol) (OLL)	Reference Standard	R124T0	R047F0 (31-DEC-2021)	2190-21-8	N/A	$837.00	SE	Chemical Synthesis		24	mg	1516200100		VIAL	No	No			Solvents
1612426	Active	Sesame Oil Related Compound B (12 mg x 2 vials) ((1,2-Dilinoleoyl-3-palmitoyl-rac-glycerol) (PLL))	Reference Standard	R164D0	R05710 (31-MAR-2023)	2190-15-0	N/A	$863.00	CA	Chemical Synthesis		24	mg	1516200100		VIAL	No	No			Solvents
1612459	Active	Sevelamer Carbonate (100 mg)	Reference Standard	F0M136		845273-93-0	N/A	$411.00	GB	Chemical Synthesis		100	mg	3911906100		VIAL	No	No			Renal
1612460	Active	Sevelamer Hydrochloride (100 mg)	Reference Standard	F0M137		152751-57-0	N/A	$432.00	GB	Chemical Synthesis		100	mg	3911906100		VIAL	No	No			Renal
1612506	Active	L-Serine (200 mg)	Reference Standard	R11570	H1J185 (31-DEC-2020)	56-45-1	N/A	$313.00	US	Plant		200	mg	2922505000		VIAL	No	No			Amino Acids
1612517	Active	Sertraline Hydrochloride Racemic Mixture (30 mg) ((1RS,4RS)-4-(3,4-Dichlorophenyl)-N-methyl-1,2,3,4-tetrahydro-1-naphthylamine hydrochloride)	Reference Standard	R176F0	R05470 (31-AUG-2024)	79617-89-3	N/A	$838.00	IN	Chemical Synthesis	UN3077	30	mg	2909191800		VIAL	No	No			Psychiatrics
1612528	Active	Sertraline Hydrochloride Related Compound A (25 mg) ((1RS,4SR)-4-(3,4-Dichlorophenyl)-N-methyl-1,2,3,4-tetrahydro-1-naphthylamine hydrochloride)	Reference Standard	R151L0	F0H425 (30-NOV-2022)	N/A	N/A	$943.00	US	Chemical Synthesis		25	mg	2921490002		VIAL	No	No			Psychiatrics
1612539	Active	Sertraline Hydrochloride (100 mg)	Reference Standard	R118W0	R050W0 (30-APR-2021)	79559-97-0	N/A	$670.00	ES	Chemical Synthesis	UN3077	100	mg	2921490002		VIAL	No	No			Psychiatrics
1612540	Active	Sevoflurane (1 mL)	Reference Standard	R187E0	R12620 (30-SEP-2025)	28523-86-6	N/A	$302.00	JP	Chemical Synthesis	UN3334	1	mL	2909191800		AMPULE	No	No			Anaesthetics
1612550	Active	Sevoflurane Related Compound A (0.2 mL) (1,1,1,3,3-Pentafluoroisopropenyl fluoromethyl ether)	Reference Standard	R15850	R056M0 (31-MAR-2023)	58109-34-5	N/A	$948.00	IN	Chemical Synthesis	UN2810	0.2	mL	2909191800		AMPULE	No	No			Anaesthetics
1612561	Active	Sildenafil Citrate (100 mg)	Reference Standard	R132W0	F0K412 (30-SEP-	171599-83-0	N/A	$551.00	US	Chemical Synthesis		100	mg	2933595960		VIAL	No	No			Cardiovascul

Status: Currently Official on 06-Jan-2024
Official Date: Official as of 01-May-2023
DOI Ref: gq5k3
DocId: GUID-15A9CB5B-39A6-46F6-85B8-56BD0BAB71C4_3_en-US
Document Type: USP
DOI: https://doi.org/10.31003/USPNF_M42840_03_01

Isoflurane



$C_3H_2ClF_5O$ 184.49
Ethane, 2-chloro-2-(difluoromethoxy)-1,1,1-trifluoro-;
1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether
CAS RN®: 26675-46-7; UNII: CYS9AKD70P.

DEFINITION

Isoflurane contains NLT 99.9% and NMT 100.0% of isoflurane ($C_3H_2ClF_5O$).

IDENTIFICATION

- **A.** The IR absorption spectrum of Isoflurane, obtained using a gas cell, exhibits maxima only at the same wavelengths as those of a similar preparation of USP Isoflurane RS.

ASSAY

- **PROCEDURE**

Analysis: Using the results from the test for *Organic Impurities*, calculate the percentage of isoflurane ($C_3H_2ClF_5O$) in the sample of Isoflurane taken by subtracting the sum of percentages for the impurities found from 100.0%.

Acceptance criteria: 99.9%–100.0%

IMPURITIES

- **CHLORIDE**

Sample solution: Pipet 10 mL of Isoflurane into a suitable vessel containing 60 mL of isopropyl alcohol and 4 drops of dilute nitric acid (1:1), and stir to dissolve.

Analysis: Titrate potentiometrically with 0.002 N silver nitrate in isopropyl alcohol VS.

Acceptance criteria: NMT 2.11 mL is required (NMT 10 ppm)

- **LIMIT OF FLUORIDE**

Use plasticware throughout this test.

Buffer: Dissolve 110 g of sodium chloride and 1 g of sodium citrate in 700 mL of water in a 2-L volumetric flask. Cautiously add 150 g of sodium hydroxide, and dissolve with shaking. Cool to room temperature, and, while stirring, cautiously add 450 mL of glacial acetic acid to the cooled solution. Cool, add 600 mL of isopropyl alcohol, dilute with water to volume, and mix. The pH of this solution is between 5.0 and 5.5. [NOTE—This solution may be used for 6 weeks if stored at room temperature.]

Solution A: Transfer 55 mg of USP Sodium Fluoride RS to a 25-mL volumetric flask. Add 5 mL of water, and mix to dissolve. Add 1.0 mL of 0.0025 N sodium hydroxide, dilute with water to volume, and mix. Each mL of this solution contains 1 mg of fluoride ion. Store in a tightly closed plastic container. [NOTE—This solution may be used for 2 weeks if stored in a refrigerator.]

Standard stock solution 1: 2.0 µg/mL of fluoride in water from *Solution A*

Standard stock solution 2: 6.0 µg/mL of fluoride in water from *Solution A*

Standard stock solution 3: 10.0 µg/mL of fluoride in water from *Solution A*

Standard stock solution 4: 20.0 µg/mL of fluoride in water from *Solution A*

Standard solution 1: 1.0 µg/mL of fluoride in *Buffer* from *Standard stock solution 1*

Standard solution 2: 3.0 µg/mL of fluoride in *Buffer* from *Standard stock solution 2*

Standard solution 3: 5.0 µg/mL of fluoride in *Buffer* from *Standard stock solution 3*

Standard solution 4: 10.0 µg/mL of fluoride in *Buffer* from *Standard stock solution 4*

Sample solution: Shake 50.0 mL of Isoflurane with 50.0 mL of water for 5 min, and allow the liquids to separate completely. Transfer 25.0 mL of the water layer to a 50-mL volumetric flask, dilute with *Buffer* to volume, and mix.

Analysis

Samples: *Standard solutions 1–4* and *Sample solution*

(See *pH* ⟨791⟩.)

Concomitantly measure the potentials in mV, of *Standard solutions 1–4* and the *Sample solution* with a pH meter capable of a minimum reproducibility of ±0.2 mV and equipped with a fluoride ion electrode and a glass-sleeved calomel reference electrode or a double-junction fluoride ion-selective combination electrode. When taking measurements, immerse the electrodes in the solution under test, which has been transferred to a 150-mL beaker containing a polytef-coated stirring bar. Allow to stir on a magnetic stirrer with an insulated top until equilibrium is attained (1–2 min), and record the potential. Rinse and dry the electrodes between measurements, taking care to avoid damaging the crystal of the fluoride ion electrode.

A satisfactory response is achieved if the difference in potential between the potentials obtained with *Standard solution 1* and *Standard solution 4*, having fluoride concentrations of 1.0 and 10.0 µg/mL, respectively, is in the range of 50–60 mV. Plot the logarithm of the fluoride ion concentrations, in µg/mL, of *Standard solutions 1–4* versus potential, in mV. From the measured potential of the *Sample solution* and the standard response line, determine the concentration, in µg/mL, of fluoride in the *Sample solution*.

Acceptance criteria: NMT 5 µg/mL of fluoride in the *Sample solution* [NMT 0.001% (w/v) fluoride in Isoflurane]

- **NONVOLATILE RESIDUE**

Analysis: Transfer 10.0 mL of Isoflurane to a suitable weighed evaporating dish, evaporate with the aid of a current of air or stream of nitrogen to dryness, and dry the residue at 50° for 2 h.

Acceptance criteria: The weight of the residue does not exceed 2.0 mg.

Change to read:

- **ORGANIC IMPURITIES**

Standard stock solution: To a suitable tared vial, fitted with a septum, add 20 mL (29.8 g) of Isoflurane. Seal and reweigh the vial to determine the weight of the Isoflurane added. To this vial sequentially add 20 µL (30 mg) of USP Isoflurane Related Compound A RS, 21 µL (30 mg) of USP Isoflurane Related Compound B RS, and 38 µL (30 mg) of USP Acetone RS. Record the weight after the addition of each impurity and determine the total weight.

Calculate the percentage of each impurity in the *Standard stock solution*:

$$\text{Result} = (W_I/W_T) \times P_I$$

W_I = weight of each impurity added (g)
W_T = total weight of the *Standard stock solution* (g)
P_I = purity of each impurity added (%)

Standard solution: To a suitable tared vial, fitted with a septum, add 10 mL (15 g) of Isoflurane. Seal and reweigh the vial to determine the weight of the Isoflurane added.

Status: Currently Official on 06-Jan-2024
Official Date: Official as of 01-May-2023
DOI Ref: gq5k3
DocId: GUID-15A9CB5B-39A6-46F6-85B8-56BD0BAB71C4_3_en-US
Document Type: USP
DOI: https://doi.org/10.31003/USPNF_M42840_03_01

To this vial add 300 µL of the *Standard stock solution*, and record the weight to determine the weight of the *Standard stock solution* added and the final weight of the *Standard solution*.

Calculate the spiked concentration (C_S) of each impurity in the *Standard solution*:

$$\text{Result} = (W_I/W_T) \times C_I$$

W_I = weight of the *Standard stock solution* added (g)
W_T = total weight of the *Standard solution* (g)
C_I = concentration of each impurity in the *Standard stock solution* (%)

System suitability solution: To a suitable vial, fitted with a septum, add 10 mL (15 g) of Isoflurane. Seal the vial. To this vial add 100 µL of the *Standard stock solution*.

Sample solution: Isoflurane

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: GC
Detector: Flame ionization
Column: 0.32-mm × 60-m; fused-silica capillary coated with a 1.0-µm film of G16
Carrier gas: Helium
Flow rate: 1.7 mL/min (constant flow mode)
Temperatures
Injection port: 175°
Detector: 200°
Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	—	40	8
40	10	170	4

Injection volume: 2 µL
Injection type: Split; split ratio, 23:1

System suitability
Samples: *Standard solution* and *System suitability solution*
Suitability requirements
Tailing factor: NMT 1.5 for acetone, *Standard solution*
Relative standard deviation: NMT 5% each for isoflurane related compound A, isoflurane related compound B, and acetone, *Standard solution*
Signal-to-noise ratio: NLT 15 for isoflurane related compound B, *System suitability solution*

Analysis: Injections of Isoflurane used to prepare the *Standard solution* must be made to estimate the amount of known impurities that may be present in the solvent. The final concentration of each impurity is equal to the concentration of the impurity added plus the concentration inherent in the matrix.
Samples: *Standard solution* and *Sample solution*
Calculate the final concentration (C_F) of each impurity in the *Standard solution*:

$$\text{Result} = [r_U/(r_S - r_U) \times C_S] + C_S$$

r_U = peak response of each impurity from the isoflurane used as the solvent
r_S = peak response of each impurity from the *Standard solution*
C_S = spiked concentration of each impurity in the *Standard solution* (%)

Calculate the percentage of isoflurane related compound A, isoflurane related compound B, and acetone observed in the *Sample solution*:

$$\text{Result} = (r_U/r_S) \times C_F$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of each impurity from the *Standard solution*
C_F = final concentration of each impurity in the *Standard solution* (%)

Calculate the percentage of all other impurities:

$$\text{Result} = (r_U/r_S) \times {}^{\blacktriangle}C_{F\blacktriangle\,(\text{ERR 1-May-2023})} \times (1/F)$$

r_U = peak response of the impurity from the *Sample solution*
r_S = peak response of isoflurane related compound B from the *Standard solution*
${}^{\blacktriangle}C_{F\blacktriangle\,(\text{ERR 1-May-2023})}$ = final concentration of USP Isoflurane Related Compound B RS in the *Standard solution* (%)
F = relative response factor relative to isoflurane related compound B (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time[a]	Relative Response Factor[b]	Acceptance Criteria, NMT (%)
Dichloroisoflurane[c]	0.41	0.28	0.003
Isoflurane isomer[d]	0.43	0.87	0.003
Isoflurane related compound A	0.46	—	0.01
Isoflurane related compound B	0.56	1.00	0.007
Chloroisoflurane[e]	0.59	0.35	0.003
Acetone	0.79	—	0.008
Isoflurane	1.00	—	—
Any individual unspecified impurity	—	1.00	0.003
Total impurities	—	—	0.1

[a] Relative to isoflurane.
[b] Relative to isoflurane related compound B.
[c] 1,1-Dichloro-1-(chlorodifluoromethoxy)-2,2,2-trifluoroethane.
[d] 2-(Chlorodifluoromethoxy)-1,1,1-trifluoroethane.
[e] 1,1-Dichloro-1-(difluoromethoxy)-2,2,2-trifluoroethane.

SPECIFIC TESTS

- **REFRACTIVE INDEX** ⟨831⟩: 1.2990–1.3005 at 20°
- **WATER DETERMINATION** ⟨921⟩, *Method I*: NMT 0.10%
- **ACIDITY OR ALKALINITY**

Sample: Transfer 5 mL of Isoflurane and 2 mL of carbon dioxide-free water to a 10-mL glass-stoppered graduated cylinder, shake for 3 min, and allow the layers to separate.
Analysis: Test the aqueous layer (upper) with both red litmus paper and blue litmus paper.
Acceptance criteria: The aqueous layer is neutral to litmus paper. The aqueous phase should not turn the red litmus paper blue, nor should it turn the blue litmus paper red.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature. Replace the cap securely after each use.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Acetone RS
  USP Isoflurane RS
  USP Isoflurane Related Compound A RS
  1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether.
  $C_3HCl_2F_5O$ 218.94
  USP Isoflurane Related Compound B RS
  2,2,2-Trifluoroethyl difluoromethyl ether.
  $C_3H_3F_5O$ 150.05
  USP Sodium Fluoride RS

Sevoflurane

$C_4H_3F_7O$ 200.05

Propane, 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-;
Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether
CAS RN®: 28523-86-6; UNII: 38LVP0K73A.

DEFINITION

Sevoflurane contains NLT 99.97% and NMT 100.00% of sevoflurane ($C_4H_3F_7O$).

IDENTIFICATION

• **A. Infrared Absorption**

Acceptance criteria: The IR absorption spectrum of Sevoflurane, obtained using a gas cell, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Sevoflurane RS.

ASSAY

• **Procedure**

Analysis: Using the results from the test for *Organic Impurities*, calculate the percentage of sevoflurane ($C_4H_3F_7O$) in the volume of Sevoflurane taken by subtracting the sum of percentages for all impurities found from 100.00%.

Acceptance criteria: 99.97%–100.00%

IMPURITIES

• **Limit of Fluoride**

[Note—Use plastic utensils throughout this test.]

Buffer solution: Transfer 110 g of sodium chloride and 1 g of sodium citrate to a 2000-mL volumetric flask. Dissolve in 700 mL of water. Carefully add 150 g of sodium hydroxide, and shake to dissolve. Cool to room temperature, and carefully add 450 mL of glacial acetic acid while stirring. Cool, add 600 mL of isopropyl alcohol, and dilute with water to volume. [Note—The pH of this solution is 5.0–5.5. This solution may be used for 6 weeks when stored at room temperature.]

Solution A: Transfer 221 mg of sodium fluoride, previously dried at 150° for 4 h, to a 100-mL volumetric flask. Add about 20 mL of water, and mix to dissolve. Add 1.0 mL of 0.01 N sodium hydroxide, and dilute with water to volume. Each mL of this solution contains 1 mg of fluoride. Store in a tightly closed, plastic container. [Note—This solution may be used for 2 weeks when stored in a refrigerator.]

Standard stock solution 1: 0.2 µg/mL of fluoride from *Solution A* in water

Standard stock solution 2: 0.5 µg/mL of fluoride from *Solution A* in water

Standard stock solution 3: 2 µg/mL of fluoride from *Solution A* in water

Standard stock solution 4: 5 µg/mL of fluoride from *Solution A* in water

Standard solution 1: 0.10 µg/mL of fluoride from *Standard stock solution 1* in *Buffer solution*

Standard solution 2: 0.25 µg/mL of fluoride from *Standard stocksolution 2* in *Buffer solution*

Standard solution 3: 1.0 µg/mL of fluoride from *Standard stocksolution 3* in *Buffer solution*

Standard solution 4: 2.5 µg/mL of fluoride from *Standard stocksolution 4* in *Buffer solution*

Sample solution: Pipet 50.0 mL of Sevoflurane and 50.0 mL of water into a separatory funnel, shake vigorously for 3 min, and allow the liquids to separate completely. Transfer 25.0 mL of the aqueous top layer to a 50-mL volumetric flask, and dilute with *Buffer solution* to volume.

Analysis

Samples: *Standard solutions 1–4* and *Sample solution*

Concomitantly measure the potentials, in mV, of *Standard solutions 1–4* and the *Sample solution* with a pH meter (see *pH* ⟨791⟩) capable of a minimum reproducibility of ±0.2 mV, and equipped with a fluoride-specific ion-indicating electrode and a glass-sleeved calomel reference electrode. When taking measurements, transfer the solution under test to a 100-mL beaker containing a polytef-coated stirring bar, and immerse the electrodes. Allow to stir on a magnetic stirrer having an insulated top until equilibrium is attained in about 2–3 min, and record the potential. Rinse the electrodes with the *Buffer solution*, and dry, taking care to avoid damaging the crystal of the specific-ion electrode. A satisfactory response is achieved if the difference between the potentials obtained with *Standard solution 4* and *Standard solution 2* is in the range between 50 and 60 mV. Plot the logarithms of the fluoride concentrations, in µg/mL, of *Standard solutions 1–4* versus potentials, in mV. From the graph and the measured potential of the *Sample solution*, determine the concentration, *C* (µg/mL) of fluoride in the *Sample solution*. Multiply *C* by 2 to obtain the concentration (µg/mL) of fluoride in the portion of Sevoflurane taken.

Acceptance criteria: NMT 2 µg/mL is found.

• **Limit of Nonvolatile Residue**

Analysis: Transfer 10.0 mL of Sevoflurane to an evaporating dish, evaporate to dryness on a steam bath, and dry the residue at 105° for 2 h.

Acceptance criteria: The weight of the residue does not exceed 1.0 mg.

• **Organic Impurities**

Internal standard solution: Use dimethoxymethane.

Ethylene dichloride identification solution: Transfer 2.0 mL of Sevoflurane to a vial, and seal with a cap and septum. Using a microsyringe, add 20 µL of ethylene dichloride through the septum of the vial, and mix thoroughly.

Sevoflurane related compounds stock solution: Transfer 20 mL of Sevoflurane to a 40-mL vial with a septum lid. Add 20 µL each of USP Sevoflurane Related Compound A RS, USP Sevoflurane Related Compound B RS, and USP Sevoflurane Related Compound C RS to the vial, and mix thoroughly.

Related compounds identification solution: Transfer 1.0 mL of *Ethylene dichloride identification solution* to a 10-mL volumetric flask, and dilute with Sevoflurane to volume. Transfer 2 mL of this solution and 5 mL of *Sevoflurane related compounds stock solution* to a 50-mL volumetric flask, dilute with Sevoflurane to volume, and mix thoroughly.

Standard solutions: Prepare in duplicate, proceeding for each as follows. Transfer 2.0 mL of ethylene dichloride to a screw-capped vial, immediately seal with a cap and septum, and place on a balance. Using a microsyringe, transfer about 20 µL of USP Sevoflurane RS to the vial by inserting the syringe needle through the septum. Record the quantity, in mg, of USP Sevoflurane RS added. Using the same method, transfer about 20 µL of the *Internal standard solution* to the vial, and record the quantity, in mg, of the solution added.

Control standard solution: Place a 40-mL vial with a septum lid on an analytical balance, and tare out the weight. Add 30 mL of ethylene dichloride to the vial, and seal tightly. Record the weight of the ethylene dichloride, and tare. Using a microsyringe, add 20 µL of the USP Sevoflurane RS through the septum of the vial, record the

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weight, and mix thoroughly. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, and dilute with ethylene dichloride to volume.

Sample solution: Transfer 20.0 mL of Sevoflurane to a vial, and insert the stopper. Using a microsyringe, add 5 µL of the *Internal standard solution* to the vial.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m fused-silica capillary column coated with a 3.0-µm film of liquid phase G43

Temperatures

Injection port: 200°

Detector: 225°

Column: See *Table 1*. Before use, condition the column overnight at a temperature of 250°.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	0	40	10
40	10	200	14

Carrier gas: Helium

Flow rate: 1 mL/min. [NOTE—The make-up gas flow rate is 20 mL/min.]

Injection volume: 2 µL

Injection type: Split ratio 1:20

System suitability

Samples: *Related compounds identification solution* and one of the *Standard solutions*

Suitability requirements

[NOTE—Identify the peaks using the relative retention times given in *Table 2*.]

Resolution: NLT 2.0 between sevoflurane related compound C and ethylene dichloride, *Related compounds identification solution*

Column efficiency: NLT 6000 theoretical plates for the sevoflurane peak, *Standard solution*

Relative standard deviation: NMT 3.0% from the peak area ratio of sevoflurane to the internal standard, *Standard solution*

Analysis

Samples: *Ethylene dichloride identification solution*, *Standard solutions*, *Control standard solution*, and *Sample solution*

Calculate the response factor for each of the *Standard solutions*:

$$\text{Result} = (W_I/W_S) \times R_S$$

W_I = weight of the internal standard in the *Standard solutions* (mg)

W_S = weight of USP Sevoflurane RS in the *Standard solutions* (mg)

R_S = peak area response ratio of sevoflurane to that of the internal standard from the *Standard solutions*

The response factors for the duplicate *Standard solutions* do not differ by more than 3.0% from their average.

Calculate the quantity, in µg/g, of each impurity in the portion of Sevoflurane ($C_4H_3F_7O$) taken:

$$\text{Result} = (S_1/S_2) \times (R_I/F_R) \times (1/F) \times 250$$

S_1 = specific gravity of the internal standard, 0.859

S_2 = specific gravity of sevoflurane, 1.525

R_I = peak area response ratio of the impurity to that of the internal standard from the *Sample solution*

F_R = average response factor obtained as directed above

F = respective relative response factor for the impurities (see *Table 2*)

Acceptance criteria

[NOTE—Do not include sevoflurane, the internal standard, or any peak identified as solvent carryover (ethylene dichloride). Also, disregard any peak with an area less than 30% of the average area of the principal peak from the *Control standard solution*.]

Individual impurities: NMT 25 µg/g of sevoflurane related compound A and NMT 100 µg/g of any other single impurity

Total impurities: NMT 300 µg/g

Table 2

Name	Relative Retention Time	Relative Response Factor
Sevoflurane related compound A	0.78	1.0
Sevoflurane related compound B	0.83	1.0
Sevoflurane	1.0	—
Internal standard (dimethoxymethane)	1.35	—
Ethylene dichloride	2.28	—
Sevoflurane related compound C	2.31	0.46
Unknown impurities	—	1

SPECIFIC TESTS

- **REFRACTIVE INDEX** ⟨831⟩: 1.2745–1.2760 at 20°
- **ACIDITY OR ALKALINITY:** Transfer 20.0 mL of Sevoflurane and 20.0 mL of carbon dioxide-free water to a separatory funnel, shake for 3 min, and allow the layers to separate.

  Acceptance criteria: The aqueous layer requires NMT 0.10 mL of 0.010 N sodium hydroxide or NMT 0.60 mL of 0.010 N hydrochloric acid for neutralization, bromocresol purple TS being used as the indicator.
- **WATER DETERMINATION,** *Method I* ⟨921⟩: NMT 0.1%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature. Replace the cap securely after each use.
- **USP REFERENCE STANDARDS** ⟨11⟩

  USP Sevoflurane RS

  USP Sevoflurane Related Compound A RS
  1,1,1,3,3-Pentafluoroisopropenyl fluoromethyl ether.
  $C_4H_2F_6O$ 180.05

  USP Sevoflurane Related Compound B RS
  1,1,1,3,3,3-Hexafluoro-2-methoxy-propane.
  $C_4H_4F_6O$ 182.06

  USP Sevoflurane Related Compound C RS
  1,1,1,3,3,3-Hexafluoro-2-propanol.
  $C_3H_2F_6O$ 168.04

RENCANA KEBUTUHAN REFERENCE STANDARD UNTUK PENGUJIAN RUTIN

RS Isoflurane

No.	Penggunaan	Kebutuhan/Analisa	Jumlah Analisa	Kebutuhan/Tahun	Kebutuhan/Tahun
1	Identifikasi IR dan pembakuan WS Isoflurane	1 mL	2	2 mL	2.00 vial

RS Sevoflurane

No.	Penggunaan	Kebutuhan/Analisa	Jumlah Analisa	Kebutuhan/Tahun	Kebutuhan/Tahun
1	Identifikasi IR dan pembakuan WS Sevoflurane	1 mL	2	2 mL	2.00 vial