Standard Calcium Solution for Atomic Absorption Spectrophotometry Weigh accurately 0.250 g of calcium carbonate, and add 1 mol/L hydrochloric acid TS to make exactly 100 mL. Each mL of this solution contains 1.00 mg of calcium (Ca).

Standard Copper Solution Pipet 10 mL of Standard Copper Stock Solution, dilute with water to make exactly 1000 mL: 1 mL of this solution contains 0.01 mg of copper (Cu). Prepare before use.

Standard Copper Stock Solution Weigh exactly 1.000 g of copper (standard reagent), add 100 mL of dilute nitric acid, and dissolve by heating. After cooling, add water to make exactly 1000 mL.

Standard Cyanide Stock Solution Dissolve 2.5 g of potassium cyanide in water to make exactly 1000 mL. Measure exactly 100 mL of this solution, add 0.5 mL of 4-dimethylaminobenzylidene rhodanine TS, and titrate with 0.1 mol/L silver nitrate VS until the solution shows a red color.

Each mL of 0.1 mol/L silver nitrate VS = 5.204 mg of CN

Standard Cyanide Solution Measure exactly a volume of Standard Cyanide Stock Solution, equivalent to 10 mg of cyanide (CN), add 100 mL of sodium hydroxide TS and water to make exactly 1000 mL: 1 mL of this solution contains 0.01 mg of cyanide (CN). Prepare before use.

Standard Fluorine Solution See the Oxygen Flask Combustion Method.

Standard Gold Stock Solution Dissolve 0.209 g of hydrogen tetrachloroaurate (III) tetrahydrate, exactly weighed, in 2 mL of aqua regia, heat on a water bath for 10 minutes, and add 1 mol/L hydrochloric acid TS to make exactly 100 mL: 1 mL of this solution contains 1.00 mg of gold (Au).

Standard Gold Solution for Atomic Absorption Spectrophotometry To 25 mL of Standard Gold Stock Solution, exactly measured, add water to make exactly 1000 mL: 1 mL of this solution contains 0.025 mg of gold (Au).

Standard Iron Solution Weigh exactly 86.3 mg of ammonium iron (III) sulfate 12-water, dissolve in 100 mL of water, and add 5 mL of dilute hydrochloric acid and water to make exactly 1000 mL: 1 mL of this solution contains 0.01 mg of iorn (Fe).

Standard Lead Stock Solution Weigh exactly 159.8 mg of lead (II) nitrate, dissolve in 10 mL of dilute nitric acid, and add water to make exactly 1000 mL. Prepare and store this solution using glass containers, free from soluble lead salts.

Standard Lead Solution Measure exactly 10 mL of Standard Lead Stock Solution, and add water to make exactly 100 mL: 1 mL of this solution contains 0.01 mg of lead (Pb). Prepare before use.

Standard Liquids for Calibrating Viscosimeters [JIS, Standard Liquids for Calibrating Viscosimeters (Z 8809)]

Standard Mercury Solution Weigh exactly 0.0135 g of mercury (II) chloride, previously dried for 6 hours in a desiccator (silica gel), dissolve in 10 mL of dilute nitric acid, and add water to make exactly 1000 mL. Pipet 10 mL of this solution, and add 10 mL of dilute nitric acid and water to make exactly 1000 mL: 1 mL of this solution contains 0.1 μg of mercury (Hg). Prepare before use.

Standard Methanol Solution See the Methanol Test.

Standard Nickel Solution Dissolve 6.73 g of ammonium nickel (II) sulfate hexahydrate, exactly weighed, in water to make exactly 1000 mL. Pipet 5 mL of this solution, add water to make exactly 1000 mL: 1 mL of this solution contains 0.005 mg of nickel (Ni).

Standard Nitric Acid Solution Weigh exactly 0.0722 g of potassium nitrate, dissolve in water to make exactly 1000 mL: 1 mL of this solution contains 0.01 mg of nitrogen (N).

Standard Phosphoric Acid Solution Weigh exactly 0.358 g of monobasic potassium phosphate, previously dried to constant mass in a desiccator (silica gel), and add 10 mL of diluted sulfuric acid (3 in 10) and water to make exactly 1000 mL. Pipet 10 mL of this solution, and add water to make exactly 100 mL: 1 mL of this solution contains 0.025 mg of phosphoric acid (as PO_4).

Standard Potassium Stock Solution Weigh exactly 9.534 g of potassium chloride, previously dried at 130°C for 2 hours, and dissolve in water to make exactly 1000 mL: 1 mL of this solution contains 5.00 mg of potassium (K).

Standard Selenium Solution To exactly 1 mL of Standard Selenium Stock Solution add water to make exactly 1000 mL. Prepare before use. It contains 1.0 μg of selenium (Se) per mL.

Standard Selenium Stock Solution Dissolve exactly 1.405 g of selenium dioxide in 0.1 mol/L nitric acid to make exactly 1000 mL.

Standard Silver Stock Solution Dissolve 1.575 g of silver nitrate, exactly weighed, in water to make exactly 1000 mL: 1 mL of this solution contains 1.00 mg of silver (Ag).

Standard Silver Solution for Atomic Absorption Spectrophotometry Measure exactly 10 mL of Standard Silver Stock Solution, and add water to make exactly 1000 mL: 1 mL of this solution contains 0.01 mg of silver (Ag). Prepare before use.

Standard Sodium Dodecylbenzene Sulfonate Solution Weigh exactly 1.000 g of sodium dodecylbenzene sulfonate, and dissolve in water to make exactly 1000 mL. Pipet 10 mL of this solution, and add water to make exactly 1000 mL: 1 mL of this solution contains 0.01 mg of sodium dodecylbenzene sulfonate [$CH_3(CH_2)_{11}C_6H_4SO_3Na$].

Standard Sodium Stock Solution Weigh exactly 2.542 g of sodium chloride (standard reagent), previously dried at 130°C for 2 hours, and dissolve in water to make exactly 1000 mL: 1 mL of this solution contains 1.00 mg of sodium (Na).

Standard Tin Solution Weigh exactly 0.250 g of tin, and dissolve in 10 mL of sulfuric acid by heating. After cooling, transfer this solution with 400 mL of diluted hydrochloric acid (1 in 5) to a 500-mL volumetric flask, and add diluted hydrochloric acid (1 in 5) to make 500 mL. Pipet 10 mL of this solution, and add diluted hydrochloric acid (1 in 5) to make exactly 1000 mL: 1 mL of this soution contains 0.005 mg of tin (Sn). Prepare before use.

Standard Vinyl Chloride Solution Transfer about 190 mL of ethanol for gas chromotography into a 200 mL volumetric flask, and stopper with a silicone rubber stopper. Cooling this volumetric flask in a methanol-dry ice bath, inject 0.20 g of vinyl chloride, previously dried, through the silicone rubber stopper, and then inject ethanol for gas chromatography, previously cooled in a methanol-dry ice bath, through the silicone rubber stopper to make 200 mL. Then pipet 1 mL of this solution, add ethanol for gas chromatography, previously cooled in a methanol-dry ice bath, to make exactly 200 mL. Pipet 1 mL of this solution, add ethanol for gas chromatography, cooled previously in a methanol-dry ice bath to make exactly 100 mL. Preserve in a hermetic container, at a temperature not exceeding −20°C.

Standard Water-Methanol Solution See the Water Determination.

Standard Zinc Stock Solution Dissolve 1.000 g of zinc (standard reagent), exactly weighed, in 100 mL of water and 5 mL of hydrochloric acid with the aid of gentle heating, cool, and add water to make 1000 mL.

Standard Zinc Solution Measure exactly 25 mL of Standard Zinc Stock Solution, and add water to make exactly 1000 mL. Prepare before use. One mL of this solution contains 0.025 mg of zinc (Zn).

Standard Zinc Solution for Atomic Absorption Spectrophotometry See the Test for Rubber Closure for Aqueous Infusions

(5) Matching Fluids for Color

Matching Fluids for Color are prepared from the following colorimetric stock solutions. Colorimetric stock solutions are prepared by the following procedures and stored in glass-stoppered bottles. When the color of the solution is compared with Matching Fluids for Color, unless other wise specified, transfer both solutions and fluids to Nessler tubes and view transversely against a white background.

Cobalt (II) Chloride Colorimetric Stock Solution Weigh 65 g of cobalt (II) chloride hexahydrate, and dissolve in 25 mL of hydrochloric acid and water to make 1000 mL. Measure exactly 10 mL of this solution, and add water to make exactly 250 mL. Measure exactly 25 mL of the solution, add 75 mL of water and 0.05 g of mulexide-sodium chloride indicator, and add dropwise diluted ammonia solution (28) (1 in 10) until the color of the solution changes from red-purple to yellow. Titrate with 0.01 mol/L disodium dihydrogen ethylenediamine tetraacetate VS until the color of the solution changes, after the addition of diluted ammonia solution (28) (1 in 10) near the endpoint, from yellow to red-purple.

Each mL of 0.01 mol/L disodium dihydrogen ethylenediamine tetraacetate VS
= 2.3793 mg of $CoCl_2.6H_2O$

According to the titrated value, add diluted hydrochloric acid (1 in 40) to make 1 mL contains 59.5 mg of cobalt (II) chloride hexahydrate ($CoCl_2.6H_2O$: 237.93), and use this solution as the colorimetric stock solution.

Copper (II) Sulfate Colorimetric Stock Solution Weigh 65 g of copper (II) sulfate pentahydrate, and dissolve in 25 mL of hydrochloric acid and water to make 1000 mL. Measure exactly 10 mL of this solution, and add water to make exactly 250 mL. Measure exactly 25 mL of this solution, add 75 mL of water, 10 mL of a solution of ammonium chloride (3 in 50), 2 mL of diluted ammonia solution (28) (1 in 10) and 0.05 g of mulexide-sodium chloride indicator. Titrate with 0.01 mol/L disodium dihydrogen ethylenediamine tetraacetate VS until the color of the solution changes from green to purple.

Each mL of 0.01 mol/L disodium dihydrogen ethylenediamine tetraacetate VS
= 2.4969 mg of $CuSO_4.5H_2O$

According to the titrated value, add diluted hydrochloric acid (1 in 40) to make 1 mL contains 62.4 mg of copper (II) sulfate pentahydrate ($CuSO_4.5H_2O$: 249.69), and use this solution as the colorimetric stock solution.

Iron (III) Chloride Colorimetric Stock Solution Weigh 55 g of iron (III) chloride hexahydrate, and dissolve in 25 mL of hydrochloric acid and water to make 1000 mL. Measure exactly 10 mL of this solution, transfer to an iodine flask, add 15 mL of water and 3 g of potassium iodide, stopper tightly, and allow to stand in a dark place for 15 minutes. Add 100 mL of water to the mixture, and titrate the liberated iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS).

Each mL of 0.1 mol/L sodium thiosulfate VS
= 27.030 mg of $FeCl_3.6H_2O$

According to the titrated value, add diluted hydrochloric acid (1 in 4) to make 1 mL contain 45.0 mg of iron (III) chloride hexahydrate ($FeCl_3.6H_2O$: 270.30), and use this solution as the colorimetric stock solution.

Matching Fluids for Color Measure exactly the volume of colorimetric stock solutions and water shown in the following table with a buret or a pipet graduated to less than 0.1 mL, and mix.

Matching fluid for color	Parts of cobalt (II) chloride colorimetric stock solution (mL)	Parts of iron (III) chloride colorimetric stock solution (mL)	Parts of copper (II) sulfate colorimetric stock solution (mL)	Parts of water (mL)
A	0.1	0.4	0.1	4.4
B	0.3	0.9	0.3	3.5
C	0.1	0.6	0.1	4.2
D	0.3	0.6	0.4	3.7
E	0.4	1.2	0.3	3.1
F	0.3	1.2	—	3.5
G	0.5	1.2	0.2	3.1
H	0.2	1.5	—	3.3
I	0.4	2.2	0.1	2.3
J	0.4	3.5	0.1	1.0
K	0.5	4.5	—	—
L	0.8	3.8	0.1	0.3
M	0.1	2.0	0.1	2.8
N	—	4.9	0.1	—
O	0.1	4.8	0.1	—
P	0.2	0.4	0.1	4.3
Q	0.2	0.3	0.1	4.4
R	0.3	0.4	0.2	4.1
S	0.2	0.1	—	4.7
T	0.5	0.5	0.4	3.6

(6) Optical Filters for Wavelength and Transmission Rate Calibration

Use optical filters for wavelength calibration and those for transmission rate calibration shown in Table 1 and Table 2, respectively. The optical filters for transmission rate calibration are also used for the calibration of absorbances.

Table 1. Optical Filters for Wavelength Calibration

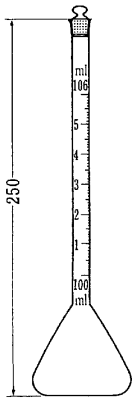
Type of filter	Range of wavelength calibration (nm)	Product name
Neodymium optical filter for wavelength calibration	400 - 750	JCRM 001
Holmium optical filter for wavelength calibration	250 - 600	JCRM 002

Table 2. Optical Filters for Transmission Rate Calibration

Type of filter	Transmission rate for calibration (%)	Product name
Optical filter for calibration within the visible wavelength range	1	JCRM 101
	10	JCRM 110
	20	JCRM 120
	30	JCRM 130
	40	JCRM 140
	50	JCRM 150
Optical filter for calibration within the ultraviolet wavelength range	10	JCRM 210 A
	30	JCRM 230 A
	50	JCRM 250 A
Optical filter for calibration within the near-ultraviolet wavelength range	10	JCRM 310
	30	JCRM 330
	50	JCRM 350

(7) Measuring Instruments, Appliances

Balances and masses (1) Chemical balances—Use balances readable to the extent of 0.1 mg.



The figures are in mm.

Fig. 1

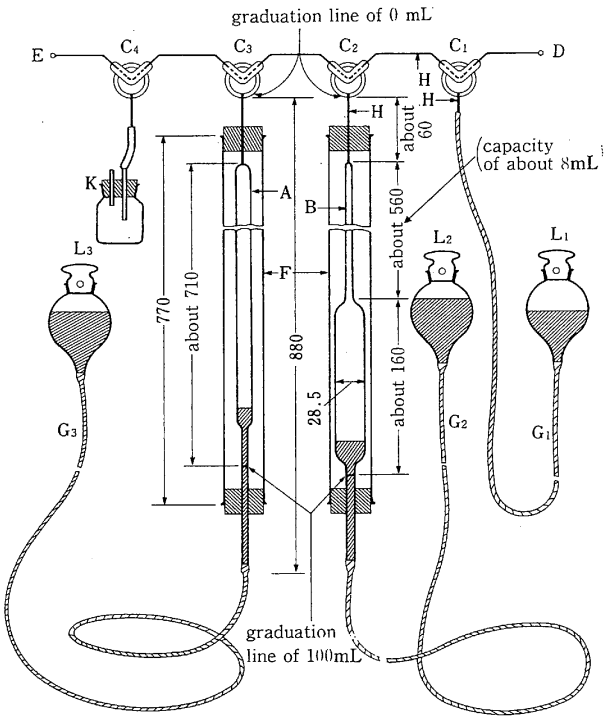
(2) Semimicrobalances—Use balances readable to the extent of 0.01 mg.

(3) Microbalances—Use balances readable to the extent of 0.001 mg.

(4) Masses—Use calibrated masses.

Cassia flask Use glass-stoppered flasks, shown in Fig. 1, made of hard glass and having graduation lines of volume on the neck.

Gas mixer Use the apparatus, shown in Fig. 2, made of hard glass.



The figures are in mm.

Fig. 2

A: Gas buret (capacity of 100 mL, about 13.7 mm in inside diameter, graduated in 0.2 mL divisions, and graduated in 0.1 mL divisions at the lower, narrow part).

B: Gas buret (capacity of 100 mL, about 4.2 mm in inside diameter at the upper stem with graduation in 0.02-mL division, about 28.5 mm in inside diameter at the lower stem with graduation in 1-mL divisions).

C: (C_1, C_2, C_3 and C_4): Three-way stopcock.

D: Inlet of sample (bent forward at 20 mm in length).

E: Outlet of mixed gas (bent forward at 20 mm in length).

F: Jacket (about 770 mm in length, about 40 mm in outside diameter, almost completely filled with water at room temperature).

G: Rubber pressure tubing, about 4 mm in inside diameter (G_1: about 80 cm in length; G_2 and G_3: about 120 cm in length).

H: Heavy-wall capillary tube (about 1 mm in inside diameter).

K: Receiver.

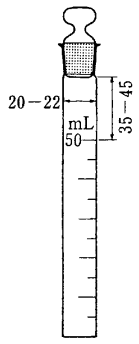
L: Leveling bulb (L_1: filled with about 50 mL of mercury; L_2 and L_3: filled with about 150 mL of mercury).

Nessler tube Use colorless, glass-stoppered cylinders 1.0 to 1.5 mm in thickness, shown in Fig. 3, made of hard glass. The difference of the height of the graduation line of 50 mL from the bottom among cylinders does not exceed 2 mm.

Sieves Sieves conform to the specifications in the following table. Use the sieve number of nominal size as the designation.

Thermometers Ordinarily, use calibrated thermometers with an immersion line (rod) or calibrated total immersion mercury-filled thermometers according to the Japanese Industrial Standards. Use the thermometers with the immersion line (rod), shown in the following table, for the tests in Congealing Point, Melting Point (Method 1), Boiling Point and Distilling Range.

Volumetric measures Use volumetric flasks, pipets, burets and measuring cylinders conforming to the Japanese Industrial Standard.



The figures are in mm.

Fig. 3

Sieve number	Nominal size (μm)	Specification of sieves				
		Sieve opening (mm)			Wire (mm)	
		Size (mm)	Permissible variation		Diameter	Permissible variation
			Average	Maximum		
3.5	5600	5.60	±0.14	0.42	1.66	±0.040
4	4750	4.75	±0.118	0.41	1.60	±0.040
4.7	4000	4.00	±0.100	0.37	1.40	±0.040
5.5	3350	3.35	±0.100	0.32	1.27	±0.030
6.5	2800	2.80	±0.084	0.28	1.11	±0.030
7.5	2360	2.36	±0.070	0.24	1.03	±0.030
8.6	2000	2.00	±0.060	0.20	0.953	±0.030
10	1700	1.70	±0.051	0.17	0.840	±0.025
12	1400	1.40	±0.042	0.14	0.717	±0.025
14	1180	1.18	±0.035	0.14	0.634	±0.025
16	1000	1.00	±0.030	0.14	0.588	±0.025
18	850	0.850	±0.034	0.127	0.523	±0.025
22	710	0.710	±0.028	0.112	0.450	±0.025
26	600	0.600	±0.024	0.101	0.390	±0.020
30	500	0.500	±0.020	0.089	0.340	±0.020
36	425	0.425	±0.017	0.081	0.290	±0.020
42	355	0.355	±0.013	0.072	0.250	±0.020
50	300	0.300	±0.012	0.065	0.208	±0.015
60	250	0.250	±0.0099	0.058	0.173	±0.015
70	212	0.212	±0.0087	0.052	0.151	±0.015
83	180	0.180	±0.0076	0.047	0.126	±0.015
100	150	0.150	±0.0066	0.043	0.104	±0.015
119	125	0.125	±0.0058	0.038	0.088	±0.015
140	106	0.106	±0.0052	0.035	0.075	±0.010
166	90	0.090	±0.0046	0.032	0.063	±0.010
200	75	0.075	±0.0041	0.029	0.052	±0.010
235	63	0.063	±0.0037	0.026	0.045	±0.005
282	53	0.053	±0.0034	0.024	0.037	±0.005
330	45	0.045	±0.0034	0.022	0.032	±0.005
391	38	0.038	±0.0026	0.018	0.027	±0.005

Thermometers

	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
Liquid	Mercury	Mercury	Mercury	Mercury	Mercury	Mercury
Gas filled above liquid	Nitrogen	Nitrogen	Nitrogen	Nitrogen	Nitrogen	Nitrogen
Temperature range	−17 - 50°C	40 - 100°C	90 - 150°C	140 - 200°C	190 - 250°C	240 - 320°C
Minimum graduation	0.2°C	0.2°C	0.2°C	0.2°C	0.2°C	0.2°C
Longer graduation lines at	each 1°C	each 1°C	each 1°C	each 1°C	each 1°C	each 1°C
Graduation numbered at	each 2°C	each 2°C	each 2°C	each 2°C	each 2°C	each 2°C
Total length (mm)	280 - 300	280 - 300	280 - 300	280 - 300	280 - 300	280 - 300
Stem diameter (mm)	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1
Bulb length (mm)	12 - 15	12 - 15	12 - 15	12 - 15	12 - 15	12 - 15
Distance from bottom of bulb to graduation at the lowest temperature (mm)	75 - 90	75 - 90	75 - 90	75 - 90	75 - 90	75 - 90
Distance from top of thermometer to graduation at the highest temperature (mm)	35 - 50	35 - 50	35 - 50	35 - 50	35 - 50	35 - 50
Distance from bottom of bulb to immersion line (mm)	60	60	60	60	60	60
Form of top of thermometer	loop	loop	loop	loop	loop	loop
Maximum scale error at any point	0.2°C	0.2°C	0.2°C	0.2°C	0.2°C	0.4°C

71. Sterilization and Aseptic Manipulation, and Reverse Osmosis-Ultrafiltration

(1) Sterilization and Aseptic Manipulation

1. Sterilization

Sterilization means a process whereby the killing or removal of all living microorganisms is accomplished. Generally, the sterilization process requires the choice of appropriate procedure and accurately controlled operation and conditions depending on the kind of microorganism, the conditions of contamination and the quality and nature of the substance to be sterilized.

The adequacy of sterilization is decided by means of the sterility test.

The procedure for sterilization should be carried out after confirming that the temperature, pressure, etc. are adequate for the desired sterilization.

For the choice of the conditions for sterilization or verification of the integrity of sterilization, biological indicators suitable for individual conditions of sterilization may be used.

2. Aseptic manipulation

Aseptic manipulation is a technique used for processing the sterile drug products which are not terminally sterilized in their final containers, and applied to a series of aseptic processing of the sterile products which are prepared by the filtration sterilization and/or with sterile raw materials.

Generally, aseptic manipulation requires the presterilization of all equipments and materials used for processing the sterile products, and then the products are processed in a way to give a defined sterility assurance level in the aseptic processing facilities where microbial and particulate levels are adequately maintained.

(2) Reverse Osmosis-Ultrafiltration

The Reverse Osmosis-Ultrafiltration is a water filtration method by means of crucial flow filtration utilizing either a reverse osmotic membrane or an ultrafilter, or an apparatus combining both.

When Water for Injection is prepared by the Reverse Osmosis-Ultrafiltration, pretreatment facilities, facilities for preparation of water for injection, and facilities for supplying water for injection are usually used. The pretreatment facilities, placed before the preparation facilities, are used to remove solid particles, dissolved salts and colloids in original water, so as to reduce load on the preparation facilities. They are assemblies having a cohesion apparatus, precipitation-separation apparatus, filtration apparatus, chlorine sterilization apparatus, oxidation-reduction apparatus, residual chlorine removing apparatus, precise filtration apparatus, reverse osmosis apparatus, ultrafiltration apparatus, ion exchange apparatus, etc., which are combined properly depending upon the quality of original water. The facilities for preparing water for injection consist of a