SUPPLEMENT II
TO
THE JAPANESE PHARMACOPOEIA
SEVENTEENTH EDITION

Official from June 28, 2019

English Version

THE MINISTRY OF HEALTH, LABOUR AND WELFARE

Notice: This *English Version* of the Japanese Pharmacopoeia is published for the convenience of users unfamiliar with the Japanese language. When and if any discrepancy arises between the Japanese original and its English translation, the former is authentic.

Printed in Japan

The Ministry of Health, Labour and Welfare Ministerial Notification No. 49

Pursuant to Paragraph 1, Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, 1960), this notification stated that a part of the Japanese Pharmacopoeia was revised as follows*.

NEMOTO Takumi
The Minister of Health, Labour and Welfare

June 28, 2019

A part of the Japanese Pharmacopoeia (Ministerial Notification No. 64, 2016) was revised as follows*.

(The text referred to by the term ''as follows'' are omitted here. All of the revised Japanese Pharmacopoeia in accordance with this notification (hereinafter referred to as ''new Pharmacopoeia'' in Supplement 2) are made available for public exhibition at the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, at each Regional Bureau of Health and Welfare, and at each Prefectural Office in Japan).

Supplementary Provisions

(Effective Date)

Article 1 This Notification is applied from June 28, 2019.

(Transitional measures)

Article 2 In the case of drugs which are listed in the Japanese Pharmacopoeia (hereinafter referred to as ''previous Pharmacopoeia'') [limited to those listed in new Pharmacopoeia] and drugs which have been approved as of June 28, 2019 as prescribed under Paragraph 1, Article 14 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices [including drugs the Minister of Health, Labour and Welfare specifies (the Ministry of Health and Welfare Ministerial Notification No. 104, 1994) as of June 27, 2019 as those exempted from marketing approval pursuant to Paragraph 1, Article 14 of the same law (hereinafter referred to as ''drugs exempted from approval'')], the Standards established in the previous Pharmacopoeia (limited to part of the Standards for the drugs concerned) may be accepted to conform to the Standards established in the new Pharmacopoeia before and on December 31, 2020. In the case of drugs which are listed in the new Pharmacopoeia (excluding those listed in the previous Pharmacopoeia) and drugs which have been approved as of June 28, 2019 as prescribed under the Paragraph 1, Article 14 of the same law (including those exempted from approval), they may be accepted as those being not listed in the new Pharmacopoeia before and on December 31, 2020.

(Partial revision of Products Delivery Rules of National Institute of Infectious Diseases)

Article 3 Omitted.

*The term ''as follows'' here indicates the content of Supplement II to the Japanese Pharmacopoeia Seventeenth Edition from General Notice to Ultraviolet-visible Reference Spectra (pp. 2877 – 2991).

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PREFACE

The 17th Edition of the Japanese Pharmacopoeia (JP) was promulgated by Ministerial Notification No.64 of the Ministry of Health, Labour and Welfare (MHLW) on March 7, 2016.

In July 2016, the Committee on JP established the basic principles for the preparation of the JP 18th Edition, setting out the roles and characteristics of the JP, the definite measures for the revision, and the date of the revision.

It was agreed that the JP should provide an official standard, being required to assure the quality of medicines in Japan in response to the progress of science and technology and medical demands at the time. It should define the standards for specifications, as well as the methods of testing to assure overall quality of all drugs in principle, and it should have a role in clarifying the criteria for quality assurance of drugs that are recognized to be essential for public health and medical treatment.

The JP has been prepared with the aid of the knowledge and experience of many professionals in the pharmaceutical field. Therefore, the JP should have the characteristics of an official standard, which might be widely used by all parties concerned, and it should play an appropriate role of providing information and understanding about the quality of drugs to the public. Moreover, as a pharmaceutical quality standard, it should contribute promoting and maintaining of advancedness as well as international consistency and harmonization of technical requirements in the international community.

At the Committee, the five basic principles of JP, which we refer to as the ''five pillars'', were established as follows: 1) Including all drugs which are important from the viewpoint of health care and medical treatment; 2) Making qualitative improvement by introducing the latest science and technology; 3) Further promoting internationalization in response to globalization of drug market; 4) Making prompt partial revision as necessary and facilitating smooth administrative operation; and 5) Ensuring transparency regarding the revision, and disseminating the JP to the public. It was agreed that the Committee on JP should make efforts, on the basis of these principles, to ensure that the JP is used more effectively in the fields of health care and medical treatment by taking appropriate measurements, including getting the understanding and cooperation of other parties concerned.

It was also agreed that JP articles should cover drugs, which are important from the viewpoint of health care and medical treatment, clinical performance or merits and frequency of use, as soon as possible after they reach the market.

The target date for the publication of JP 18th Edition (the Japanese edition) was set as April 2021.

JP drafts are discussed in the following committees that were established in the Pharmaceuticals and Medical Devices Agency: Expert Committee; Sub-expert Committee; Sub-committee on Manufacturing Process-related Matters; Committee on Chemicals; Committee on Antibiotics; Committee on Biologicals; Committee on Crude Drugs; Committee on Pharmaceutical Excipients; Committee on Physico-Chemical Methods; Committee on Drug Formulation; Committee on Physical Methods; Committee on Biological Methods; Committee on Nomenclature for Pharmaceuticals; Committee on International Harmonization; and Committee on Reference Standards. Furthermore, working groups are established under the Expert Committee, Committee on Pharmaceutical Excipients, Committee on Physico-Chemical Methods and Committee on Drug Formulation.

The committees initiated deliberations on several revisions.

Draft revisions covering subjects in General Notices, General Rules for Preparations, General Tests, Monographs, Ultraviolet-visible Reference Spectra and Infrared Reference Spectra for which discussions were finished between April 2017 and November 2018, were prepared for a supplement to the JP 17.

Numbers of discussions in the committees to prepare the supplement drafts were as follows: Expert Committee (11, including a working group); Sub-committee on Manufacturing Process-related Matters (6), Committee on Chemicals (18), Committee on Antibiotics (3); Committee on Biologicals (7); Committee on Crude Drugs (15); Committee on Pharmaceutical Excipients (10); Committee on Physico-Chemical Methods (11, including a working group); Committee on Drug Formulation (19, including working groups); Committee on Physical Methods (7); Committee on Biological Methods (6); Committee on Nomenclature for Pharmaceuticals (5); Committee on International Harmonization (4).

It should be noted that in the preparation of the drafts for the supplement, generous cooperation was

given by the Pharmaceutical Technology Committee of the Kansai Pharmaceutical Industries Association, the Pharmacopeia and CMC Committee of the Pharmaceutical Manufacturers' Association of Tokyo, the Tokyo Crude Drugs Association, the International Pharmaceutical Excipients Council Japan, the Home Medicine Association of Japan, the Japan Kampo Medicines Manufacturers Association, the Japan Flavor and Fragrance Materials Association, the Japan Medical Plants Federation, the Japan Pharmaceutical Manufacturers Association, the Federation of Pharmaceutical Manufacturers' Association of Japan, the Parenteral Drug Association Japan Chapter, the Japan Reagent Association, the Japan Oilseeds Processors Association, the Japan Analytical Instruments Manufacturers' Association, and the Asian Society of Innovative Packaging Technology.

The draft revisions were examined by the Committee on JP in January 2019, followed by the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) in March 2019, and then submitted to the Minister of Health, Labour and Welfare. In the Committee on JP, Mitsuru Hashida took the role of chairman from January 2011 to June 2019.

In consequence of this revision, the JP 17th Edition carries 2008 articles, owing to the addition of 34 articles and the deletion of 3 articles.

The principles of description and the salient points of the revision in this volume are as follows:

1. The Supplement II to JP 17th Edition comprises the following items, in order: Notification of MHLW; Contents; Preface; General Notices, General Rules for Preparations; General Tests, Processes and Apparatus; Official Monographs; then followed by Infrared Reference Spectra and Ultraviolet-visible Reference Spectra; General Information; and as an appendix a Cumulative Index containing references to the main volume, the Supplement I and the Supplement II.

2. The articles in Official Monographs, Infrared Reference Spectra and Ultraviolet-visible Reference Spectra are respectively placed in alphabetical order in principle.

3. The following items in each monograph are put in the order shown below, except that unnecessary items are omitted depending on the nature of the drug:

(1) English title
(2) Commonly used name(s)
(3) Latin title (only for crude drugs)
(4) Title in Japanese
(5) Structural formula or empirical formula
(6) Molecular formula and molecular mass
(7) Chemical name
(8) Chemical Abstracts Service (CAS) Registry Number
(9) Origin
(10) Limits of the content of the ingredient(s) and/or the unit of potency
(11) Labeling requirements
(12) Method of preparation
(13) Manufacture
(14) Description
(15) Identification tests
(16) Specific physical and/or chemical values
(17) Purity tests
(18) Potential adulteration
(19) Loss on drying or Ignition, or Water
(20) Residue on ignition, Total ash or Acid-insoluble ash
(21) Tests being required for pharmaceutical preparations
(22) Other special tests
(23) Assay
(24) Containers and storage
(25) Shelf life
(26) Others

4. In each monograph, the following physical and chemical values representing the properties and quality of the drug are given in the order indicated below, except that unnecessary items are omitted depending on the nature of drug:

(1) Alcohol number
(2) Absorbance
(3) Congealing point
(4) Refractive index
(5) Osmolar ratio
(6) Optical rotation
(7) Constituent amino acids
(8) Viscosity
(9) pH
(10) Content ratio of the active ingredients
(11) Specific gravity
(12) Boiling point
(13) Melting point
(14) Acid value
(15) Saponification value
(16) Ester value
(17) Hydroxyl value
(18) Iodine value

5. Identification tests comprise the following items, which are generally put in the order given

below:
(1) Coloration reactions
(2) Precipitation reactions
(3) Decomposition reactions
(4) Derivatives
(5) Infrared and/or ultraviolet-visible absorption spectrometry
(6) Nuclear magnetic resonance spectrometry
(7) Chromatography
(8) Special reactions
(9) Cations
(10) Anions

6. Purity tests comprise the following items, which are generally put in the order given below, except that unnecessary items are omitted depending on the nature of drug:
(1) Color
(2) Odor
(3) Clarity and/or color of solution
(4) Acidity or alkalinity
(5) Acidity
(6) Alkalinity
(7) Chloride
(8) Sulfate
(9) Sulfite
(10) Nitrate
(11) Nitrite
(12) Carbonate
(13) Bromide
(14) Iodide
(15) Soluble halide
(16) Thiocyanate
(17) Selenium
(18) Cationic salts
(19) Ammonium
(20) Heavy metals
(21) Iron
(22) Manganese
(23) Chromium
(24) Bismuth
(25) Tin
(26) Aluminum
(27) Zinc
(28) Cadmium
(29) Mercury
(30) Copper
(31) Lead
(32) Silver
(33) Alkaline earth metals
(34) Arsenic
(35) Free phosphoric acid
(36) Foreign matters
(37) Related substances
(38) Isomer
(39) Optical isomer
(40) Polymer
(41) Residual solvent
(42) Other impurities
(43) Residue on evaporation
(44) Readily carbonizable substances

7. The following paragraphs of General Notices were revised:
(1) Paragraph 5: ''Shelf life'' in the monographs on preparations were removed from the standards for conformity, because that the stability of a pharmaceutical preparation differs depending on the formulation, type of the container and packaging and the control of the storage temperature, etc.
(2) Paragraph 13: As the cases for drug approval with the quality control using the real time-release testing (RTRT) have been accumulated, the rules of RTRT for drug release were added when RTRT is adopted as an alternative method.
(3) Paragraph 46: ''Expiration Date'' in Official Monograph was changed to ''Shelf life'' in the Supplement I to JP 17th Edition. In this revision, the rule for expression of expiration date was removed.

8. The following paragraphs were newly added to the General Rules for Preparations:
(1) The following item was newly added to the [3] Monographs for Preparations basing on the discussion about needs of this item following release of the guideline for developing liposomal formulations:
3-1-4. Liposome Injections

9. The General Rules for Preparations was revised as follows in general:
(1) [3] Monographs for Preparations: ''3-1. Injections'': the definition of ''Liposome Injections'' introduced in this revision was newly added, and ''6.17 Insoluble Particulate Matter Test for Therapeutic Protein Injections'' added to General Tests in this revision was referred and prescribed.

10. The following items were newly added to General Tests, Processes and Apparatus:
(1) 2.26 Raman Spectroscopy
(2) 2.66 Elemental Impurities – Procedures

(3) 6.16 Rheological Measurements for Semi-solid Preparations
(4) 6.17 Insoluble Particulate Matter Test for Therapeutic Protein Injections

11. The following items in General Tests, Processes and Apparatus were revised:
(1) 2.01 Liquid Chromatography
(2) 2.46 Residual Solvents
(3) 2.51 Conductivity Measurement

12. The following Reference Standards were newly added:
Bromfenac Sodium RS
L-Carnosine RS
Doripenem RS
Gatifloxacin RS
Hydroxyethylcellulose RS for Identification
Lanoconazole RS
Microcrystalline Cellulose RS for Identification
Residual Solvents Class 2C RS
Sitagliptin Phosphate RS
Sitagliptin Phosphate RS for System Suitability

13. The following Reference Standards were removed from "9.01 (2) The reference standards which are prepared by National Institute of Infectious Diseases." and added to "9.01 (1) The reference standards which are prepared by those who have been registered to prepare them by the Minister of Health, Labour and Welfare, according to the Ministerial ordinance established by the Minister separately":
Ampicillin RS
Azithromycin RS
Cefazolin RS
Cefmetazole RS
Fradiomycin Sulfate RS
Meropenem RS

14. The following substances were newly added to the Official Monographs:
Bromfenac Sodium Hydrate
Bromfenac Sodium Ophthalmic Solution
Cefalotin Sodium for Injection
Cefixime Fine Granules
Clarithromycin for Syrup
Diclofenac Sodium Suppositories
Doripenem Hydrate
Doripenem for Injection
Ethylcellulose
Felodipine
Felodipine Tablets
Gatifloxacin Hydrate
Gatifloxacin Ophthalmic Solution
Gentamicin Sulfate Injection
Gentamicin Sulfate Ointment
Hydroxyethylcellulose
Irinotecan Hydrochloride Hydrate
Lanoconazole
Lanoconazole Cream
Lanoconazole Cutaneous Solution
Lanoconazole Ointment
Minocycline Hydrochloride Granules
Nortriptyline Hydrochloride Tablets
Polaprezinc
Polaprezinc Granules
Ritodrine Hydrochloride Injection
Sitagliptin Phosphate Hydrate
Sitagliptin Phosphate Tablets
Sodium Valproate Extended-release Tablets A
Sodium Valproate Extended-release Tablets B
Telmisartan and Hydrochlorothiazide Tablets
Valsartan and Hydrochlorothiazide Tablets
Verapamil Hydrochloride Injection
Goshuyuto Extract

15. The following monographs were revised:
Amphotericin B Tablets
Beclometasone Dipropionate
Betamethasone Dipropionate
Anhydrous Dibasic Calcium Phosphate
Microcrystalline Cellulose
Chloramphenicol
Chlorpromazine Hydrochloride
Cholesterol
Cloperastine Hydrochloride
Dehydrocholic Acid
Purified Dehydrocholic Acid
Epirubicin Hydrochloride
Estriol
Etizolam
Haloperidol
Hydrocortisone
Hydrocortisone Acetate
Hydrocortisone and Diphenhydramine Ointment
Hydroxypropylcellulose
Hypromellose
Imipramine Hydrochloride
Imipramine Hydrochloride Tablets
Isomalt Hydrate
Mestranol
Methylcellulose
Methylprednisolone
Pioglitazone Hydrochloride and Glimepiride Tablets
Saccharin

Saccharin Sodium Hydrate
Light Anhydrous Silicic Acid
Sodium Fusidate
Teicoplanin
Testosterone Enanthate
Tipepidine Hibenzate Tablets
Triamcinolone Acetonide
Ursodeoxycholic Acid
Amomum Seed
Artemisia Capillaris Flower
Belladonna Root
Bitter Tincture
Bofutsushosan Extract
Boiogito Extract
Calumba
Powdered Calumba
Cassia Seed
Chrysanthemum Flower
Eucalyptus Oil
Gastrodia Tuber
Glycyrrhiza Extract
Crude Glycyrrhiza Extract
Hochuekkito Extract
Japanese Angelica Root
Powdered Japanese Angelica Root
Juzentaihoto Extract
Kakkontokasenkyushin'i Extract
Kamikihito Extract
Kamishoyosan Extract
Lithospermum Root
Lycium Bark
Nux Vomica
Oriental Bezoar
Otsujito Extract
Platycodon Root
Powdered Platycodon Root
Platycodon Fluidextract
Polygala Root
Powdered Polygala Root
Safflower
Saposhnikovia Root and Rhizome
Scopolia Rhizome
Sinomenium Stem and Rhizome
Swertia Herb
Powdered Swertia Herb
Swertia and Sodium Bicarbonate Powder
Toad Cake
Tokishakuyakusan Extract
Yokukansan Extract

16. The following monographs were deleted:
Adsorbed Habu-venom Toxoid
Freeze-dried Tetanus Antitoxin, Equine
Compound Vitamin B Powder

17. The following articles were newly added to Ultraviolet-visible Reference Spectra:
Bromfenac Sodium Hydrate
Doripenem Hydrate
Felodipine
Gatifloxacin Hydrate
Irinotecan Hydrochloride Hydrate
Lanoconazole
Sitagliptin Phosphate Hydrate

18. The following articles were newly added to Infrared Reference Spectra:
Bromfenac Sodium Hydrate
Doripenem Hydrate
Ethylcellulose
Felodipine
Gatifloxacin Hydrate
Irinotecan Hydrochloride Hydrate
Lanoconazole
Polaprezinc
Sitagliptin Phosphate Hydrate

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Supplement II to The Japanese Pharmacopoeia Seventeenth Edition

GENERAL NOTICES

Change the paragraphs 5, 13 and 46 as follows:

5. The JP Drugs are to be tested according to the provisions given in the pertinent monographs, General Notices, General Rules for Crude Drugs, General Rules for Preparations, and General Tests for their conformity to the Japanese Pharmacopoeia. However, the headings of ''Description'' and in addition ''Containers and storage'' and ''Shelf life'' in the monographs on preparations are given for information, and should not be taken as indicating standards for conformity. Nevertheless, Containers under ''Containers and storage'' in the monograph on preparations containing crude drugs as main active ingredients are the standards for conformity.

13. When an assurance that a product is of the JP Drug quality is obtained consistently from data derived from the manufacturing process validation studies, and from the records of appropriate manufacturing process control and of the test results of the quality control, the performance of some test items in the monograph at release on a product may be omitted as occasion demands. Moreover, the quality evaluation of final products (drug substances and drug products) based on in-process data including in-process testing results and monitoring data on process parameters can replace specifications and test methods in the monograph or performing the test methods, if appropriate.

46. For the JP Drugs, the contents or potency in terms of units of the active ingredient(s) in the monographs have to be shown on the immediate container or wrapping of them.

The JP Drugs are to be tested according to the provisions given in the pertinent monographs, General Notices, General Rules for Crude Drugs, General Rules for Preparations, and General Tests for their conformity to the Japanese Pharmacopoeia. (*See the General Notices 5.*)

GENERAL RULES FOR PREPARATIONS

[3] Monographs for Preparations

Change the following paragraphs:

3. Preparations for Injection

3-1. Injections

(1) Injections are sterile preparations to be administered directly into the body through skin, muscle or blood vessel, usually in form of a solution, a suspension or an emulsion of active substance(s), or of a solid that contains active substance(s) to be dissolved or suspended before use.

Parenteral Infusions, Implants/Pellets, Prolonged-Release Injections and Liposome Injections are included in this category.

(14) Unless otherwise specified, Injections and vehicles attached to preparations meet the requirements of Insoluble Particulate Matter Test for Injections <*6.07*> or Insoluble Particulate Matter Test for Therapeutic Protein Injections <*6.17*>.

Add the following next to 3-1-3. Prolonged Release Injections:

3-1-4. Liposome Injections

(1) Liposome Injections are injections to be used for intravenous administration, which are intended for improvement of in vivo stability, delivery to a target region and control of release, of active substance(s).

(2) Liposome Injections are usually prepared by using amphipathic lipid, etc. to make aqueous injections or freeze-dried injections in which closed microvesicles composed of a lipid bilayer membrane are dispersed.

(3) Liposome Injections have an appropriate function of controlled release.

(4) Liposome Injections have an appropriate particle size.

GENERAL TESTS, PROCESSES AND APPARATUS

Change the introduction to read:

General Tests, Processes and Apparatus includes common methods for tests, useful test methods for quality recognition of drugs and other articles related to them. Unless otherwise specified, acid-neutralizing capacity determination of gastrointestinal medicines, aerodynamic particle size measurement for inhalations, alcohol number determination, amino acid analysis of proteins, ammonium determination, arsenic determination, atomic absorption spectrophotometry, boiling point determination, chloride determination, conductivity measurement, congealing point determination, determination of bulk and tapped densities, digestion test, disintegration test, dissolution test, distilling range determination, elemental impurities procedures, endpoint determination in titrimetry, flame coloration, fluorometry, foreign insoluble matter test for injections, foreign insoluble matter test for ophthalmic liquids and solutions, gas chromatography, glycosylation analysis of glycoprotein, heavy metal determination, inductively coupled plasma-atomic emission spectrometry and inductively coupled plasma-mass spectrometry, infrared spectrophotometry, insoluble particulate matter test for injections, insoluble particulate matter test for ophthalmic liquids and solutions, insoluble particulate matter test for therapeutic protein injections, iron determination, laser diffraction measurement of particle size, liquid chromatography, loss on drying determination, loss on ignition determination, mass spectrometry, melting point determination, methanol determination, methods for color matching, methods of adhesion testing, microbial assay for antibiotics, mineral oil determination, nitrogen determination, nuclear magnetic resonance spectroscopy, optical rotation determination, osmolarity determination, oxygen flask combustion method, particle size determination, particle size distribution test for preparations, pH determination, powder particle density determination, qualitative test, raman spectroscopy, refractive index determination, release test for preparations for cutaneous application, residual solvents, residue on ignition determination, rheological measurements for semi-solid preparations, specific gravity and density determination, specific surface area determination, sulfate determination, test for bacterial endotoxins, test for glass containers for injections, test for metal particles in ophthalmic ointments, test for microbial limit, test for microbial limit for crude drugs, test for plastic containers, test for pyrogen, test for readily carbonizable substances, test for rubber closure for aqueous infusions, test for sterility, test for total organic carbon, test of extractable volume for injection, thermal analysis, thin-layer chromatography, turbidity measurement, ultravioletvisible spectrophotometry, uniformity of delivered dose for inhalations, uniformity of dosage units (test for content uniformity, mass variation test), viscosity determination, vitamin A assay, water determination, and X-ray powder diffraction are performed as directed in the corresponding articles under the General Tests, Processes and Apparatus. The tests for melting point of fats, congealing point of fatty acids, specific gravity, acid value, saponification value, ester value, hydroxyl value, unsaponifiable matter and iodine value of fats and fatty oils are performed as directed in the corresponding items under Fats and Fatty Oils Test, and sampling, preparation of sample for analysis, micro-scopic examination, purity test, loss on drying, total ash, acid-insoluble ash, extract content, essential oil content of crude drugs and assay of marker compounds for the assay of crude drugs and extracts of Kampo Formulations utilizing nuclear magnetic resonance (NMR) spectroscopy are performed as directed in the corresponding items under the Crude Drugs Test.

The number of each test method is a category number given individually. The number in blackets (< >) appeared in monograph indicates the number corresponding to the general test method.

2.01 Liquid Chromatography

Change the Section 7. Point to consider on changing the operating conditions as follows:

7. Point to consider on changing the operating conditions

Among the operating conditions specified in the individual monograph, inside diameter and length of the column, particle size of the packing material (pore size in the case of monolithic columns), column temperature, composition ratio of the mobile phase, composition of buffer solutions in the mobile phase, pH of the mobile phase, concentration of ion-pair forming agents in the mobile phase, ionic strength of the mobile phase, flow rate of the mobile phase, number and timing of mobile phase composition changes in gradient program, flow rate of mobile phase in gradient program, composition and flow rate of derivatizing reagents, and reaction time and chamber temperature in chemical reaction may be modified within the ranges in which the liquid chromatographic system used conforms to the requirements of system suitability.

Add the following:

2.26 Raman Spectroscopy

Raman spectroscopy is a vibrational spectroscopic technique, which evaluates a sample to be examined qualitatively or quantitatively by analyzing a spectrum obtained by dispersing very weak scattered light, having different wavelengths from irradiation light, generated when the sample is irradiated with the light. Raman scattering is observed when the polarizability of molecules changes with the vibration of chemical bonds of molecules in a sample.

Raman spectroscopy generally uses monochromatic laser light as excitation light. When the laser light is irradiated to the sample to be examined, the molecules in the sample is excited and the light with the same wavelength of the irradiation light, known as Rayleigh scattering, is scattered. The scattered light detected in the shorter wavelength side than the Rayleigh scattering is referred to as anti-Stokes scattering. The scattered light detected in the longer wavelength side than the Rayleigh scattering is referred to as Stokes scattering. Generally Stokes scattering with strong Raman scattering intensity is used for analysis. Raman spectra are usually indicated by Raman shift on the horizontal axis and Raman scattering intensity on the vertical axis.

Raman spectroscopy is capable of measuring samples (solid, semi-solid, liquid, gas, etc.) rapidly and non-destructively without pre-treatment. Application of Raman spectroscopy in the pharmaceutical field includes qualitative or quantitative evaluation of the active pharmaceutical ingredients and additives in drug substances or drug products. Raman spectroscopy can also be used for the evaluation of the physical conditions of substances, such as crystal form and crystallinity. Raman micro-spectroscopy can also be used for the evaluation of the distributions of active pharmaceutical ingredients and additives in the drug products. Furthermore, using an optical fiber probe enables it to measure the spectra of samples at a location remote from the equipment body without sampling, so that it can be used to perform pharmaceutical manufacturing process control online (or in-line).

1. Apparatus

Raman spectrometers are composed of a light source unit, a sample unit, a spectrometry unit, a detector unit, a signal processing unit, a data processing unit and a display-record-output unit. Raman spectrometers are classified into dispersive Raman spectrometers and Fourier transform Raman spectrometers according to their spectroscopic systems.

1.1. Light source

The laser which stably emits monochromatic light as excitation light to samples is used for the light source. The lasers include gas lasers such as a He-Ne laser and solid state lasers, and select a laser with wavelengths and output power according to the purpose. Pay attention to safety standards relating to a laser, when this test is performed.

1.2. Sample unit

The sample unit is composed of an optical system for collecting Raman scattering light generated by irradiation of excitation light and a sample cell. Combination of these take the form of a sample chamber, while there are apparatuses with no sample chamber, such as optical fiber probes and portable Raman spectrometers that can be carried. Representative sample chambers are macroscopic sample chambers and microscopic sample chambers. The components of these optical systems are different, respectively.

1.3. Monochromator and detector

Many dispersive Raman spectrometers use an optical filter to eliminate excitation light and use a single monochromator combined with a multichannel detector, since the configuration is simple and high sensitivity can be obtained. Detectors include multiple elements detectors and single element detectors, and general dispersive Raman spectrometers use a multiple elements detector such as a CCD detector.

Fourier transform (FT) Raman spectrometers obtain spectra by Fourier transformation of interference waveforms using an interferometer. FT-Raman spectrometers are mainly used for near infrared Raman measurement.

2. Methods Used for Measurement

The Raman spectroscopy is applicable to solid samples having a complicated shape in addition to gas/solution samples inside a glass sample cell being transparent in the visible region, using mainly light in the visible region as excitation light. In the view of the size of a measurement region and Raman scattering efficiency, an optimum optical system is selected according to the sample. The excitation wavelength, the measurement mode of the apparatus, etc. are selected and set.

2.1. Macroscopic measurement

Since the macroscopic sample chamber has a high degree of freedom in the scattering configuration, samples can be measured irrespective of solid, liquid, gas, size and shape. It is also applicable to Raman measurement under low temperature, high temperature and high pressure which require the setting of a large sample cell. Usually, in the macroscopic sample chamber three configurations: forward scattering (transmission), 90° scattering and back scattering configurations, can be usable and an appropriate scattering configuration can be selected depending on a sample.

2.2. Microscopic measurement

The microscopic sample chamber is based on an optical microscope and applicable to local analysis. In the optical system of the microscopic sample chamber a microscope objective lens works simultaneously as an excitation light converging lens and a Raman scattering light condensing lens.

Mapping measurement repeats local measurements by moving a sample or laser light position to generate a Raman image showing the two or three dimensional distribution of Raman scattering intensity. Raman images are made by using various spectral information such as a ratio of the intensity of two bands.

2.3. Probe measurement

The optical fiber probe is the collective term of the apparatus of which sample section is separated from a Raman spectrometer body by using an optical fiber and is applica-

ble to *in situ* measurement and on-line (or in-line) measurement.

2.4. Measurement by portable apparatus

The portable Raman spectrometer is possible to carry and perform analysis using Raman spectroscopy outside of laboratory. Main application of this apparatus is judgement on acceptance of pharmaceutical materials. It is used for rather simple measurement.

2.5. Points to note in measurement

Note the following points for solid, liquid and suspended samples.

(i) Measurement of solid sample: There is a possibility that the filling status, the difference in the particle diameter and the roughness of the surface of the sample could affect the scattering intensity. When measuring a crystalline sample, be careful about the effect of crystal shape. There is also a possibility that the light transparency of the sample affect the spectrum intensity. When a sample is physically and chemically inhomogeneous, it might be recommended to enlarge the spot size of laser irradiation, measure plural samples, measure the plural points of the same sample or crush the sample to homogenize.

(ii) Measurement of liquid sample: It is possible to subtract the spectrum of the solvent if there is no interaction between the solvent and the sample. When there are insoluble matters in solution, remove the matters using a filter before measurement not to obtain the Raman scattering of the matters. When a sample shows high reactivity by laser irradiation in solution, measure the sample by stirring carefully not to irradiate the same place.

(iii) Measurement of suspended sample: A suspended sample may settle, so be careful about the positioning of laser irradiation. For samples that are prone to settle, devising measurement such as optimizing the irradiation time and stirring might be helpful. When the Raman scattering of a suspended sample is weak, it is also possible to subtract the spectrum of the solvent likewise the case of measurement of a liquid sample.

3. Factors that affect spectrum

When Raman spectroscopy is applied, note the following items as factors affecting spectra.

3.1. Temperature of sample

Sample heating by laser irradiation can cause a variety of effects, such as physical form change (melting and burning) and polymorph transform. Since the chance of sample heating is increased when the spot size of laser irradiation at the sample is squeezed, be careful not to damage sample when microscopic measurement is carried out. To prevent the sample overheating, a variety of methods can be employed such as suppressing laser output, irradiating a laser without focusing and cooling a sample.

3.2. Sample characteristics

Since Raman signals are very weak, the fluorescence of a sample itself and minute impurities may interfere with Raman scattering light. Fluorescence can be reduced by choosing an excitation light source with a longer wavelength, however it should be noted that it generally decreases the intensity of the Raman scattering. Photobleaching resulted by laser irradiation before measurement, appropriate irradiation time and accumulation count may mitigate the fluorescence.

When measuring a colored sample, select the wavelength of an excitation laser depending on the absorption characteristics of the sample. When measuring a sample in a container such as, a cell for measurement, a bag or a bottle, take careful note of the spectral characteristics derived from the container in addition to the sample.

4. Control of apparatus performance

Estimate the accuracy of the wave number of Raman shift after adjusting a Raman spectrometer. Measure Raman spectra using an excitation laser utilized for actual measurement and an appropriate standard substance. Polystyrene is an example.

In the cases of 2.1., 2.2. and 2.3., make correction using at least three wave numbers among the below peak wave numbers (cm^{-1}) obtained from the spectrum of polystyrene. The number in parentheses indicates the permissible range.

620.9 (± 1.5)
1001.4 (± 1.5)
1031.8 (± 1.5)
1602.3 (± 1.5)
3054.3 (± 3.0) (Note: 3054.3 cm^{-1} cannot be measured depending on an excitation wavelength.)

In the case of 2.4., make correction in the same manner using at least three wave numbers among the below peak wave numbers (cm^{-1}).

620.9 (± 2.5)
1001.4 (± 2.0)
1031.8 (± 2.0)
1602.3 (± 3.0)

Other substance such as cyclohexane can be used as a standard substance, if it is validated.

5. Qualitative and quantitative analysis

5.1. Qualitative analysis

As Raman spectroscopy observe the vibrational energy of a molecule and can obtain a characteristic spectrum depending on the structure of a substance to be analyzed, qualitative analysis based on chemical structural information can be performed.

When the Raman spectra of a sample and the Reference Standard of a substance to be identified are compared and both spectra exhibit similar scattering intensities at the same Raman shifts, the identity of those can be confirmed.

When a sample treatment method for a solid sample is indicated in the monograph in the case of nonconformity of the scattering spectrum with that of the Reference Standard, treat the sample and the Reference Standard under the condition as directed in the monograph, then repeat the measurement.

When the characteristic scattering wave numbers of a substance to be identified are specified in the monograph, the clear appearance of the scattering of a sample at all the specified scattering wave numbers can confirm the identity of the sample with the substance to be identified.

Raman spectroscopy is also applicable to the process control of drug substances or drug products by using a score obtained from a Raman spectrum by a chemometric methodology such as principal component analysis, and characteristic peak wave numbers of the substance to be examined, as indices. Chemometrics usually means mathematical technique and statistic technique for quantization and informatization of chemical data.

5.2. Quantitative analysis

The concentrations of components of a sample to be analyzed can be calculated by calibration curves plotting the relationship between scattering intensity at a specified wave number and concentration. In the case where the composition of components of a sample is complicated, the concentrations of components in the sample can also be calculated by developing a calibration model about a spectrum measured using an existing standard sample by a chemometric methodology and applying the model to the spectrum of the sample to be examined. Chemometric methodologies for obtaining a calibration model include multiple regression analysis method and PLS (Partial least squares) regression analysis method.

The variation of peak intensity at around the reference values of wave numbers using a standard sample, polystyrene etc. used in 4., is preferable to be within ± 10% compared to that obtained in the last measurement.

2.46 Residual Solvents

Change as follows:

The chapter of residual solvents describes the control, identification and quantification of organic solvents remaining in drug substances, excipients and drug products.

I. Control of residual solvents

1. Introduction

Residual solvents in pharmaceuticals (except for crude drugs and their preparations) are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. The test method described in this chapter does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Since there is no therapeutic benefit from residual solvents, all residual solvents should be reduced to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (Class 1, Table 2.46-1) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2, Table 2.46-2) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, Table 2.46-3) should be used where practical.

Testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug products. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level equal to or below that recommended in this chapter, no testing of the drug product for residual solvents needs to be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. Drug product should also be tested if a solvent is used during its manufacture.

The limit applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as short term (30 days or less) or topical application. Justification for these levels should be made on a case by case basis.

2. General principles

2.1. Classification of residual solvents by risk assessment

The term ''PDE'' (Permitted Daily Exposure) is defined in this chapter as a pharmaceutically acceptable daily intake of residual solvents. Residual solvents assessed in this chapter were evaluated for their possible risk to human health and placed into one of three classes as follows:

(i) Class 1 solvents: Solvents to be avoided in manufacture of pharmaceuticals

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards. Class 1 solvents are listed in Table 2.46-1.

(ii) Class 2 solvents: Solvents to be limited in pharmaceuticals

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities. Class 2 solvents are listed in Table 2.46-2.

(iii) Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to human; no health-based exposure limit is needed. Class 3 solvents are listed in Table 2.46-3 and have PDEs of 50 mg or more per day.

2.2. Option for describing limits of Class 2 solvents

Two options are available when setting limits for Class 2 solvents.

2.2.1. Option 1

The concentration limits in ppm can be calculated using equation (1) below by assuming a product mass of 10 g administered daily.

$$\text{Concentration limit (ppm)} = \frac{1000 \times PDE}{\text{dose}} \quad (1)$$

Here, PDE is given in terms of mg per day and dose is given in g per day.

These limits are considered acceptable for all substances, excipients, or products. Therefore this option may be applied if the daily dose is not known or fixed. If all excipients and drug substances in a formulation meet the limits given in Option 1, then these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day should be considered under Option 2.

2.2.2. Option 2

It is not considered necessary for each component of the drug product to comply with the limits given in Option 1. The PDE in terms of mg per day as stated in Table 2.46-2 can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in drug product. Such limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, reasonable variation in the manufacturing process, and the limits should reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

3. Analytical procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. If only Class 3 solvents are present, a nonspecific method such as loss on drying may be used. The analytical method should be validated adequately.

4. Reporting levels of residual solvents

Manufacturers of drug products need certain information about the content of residual solvents in excipients or drug substances. The following statements are given as acceptable examples of the information.

(i) Only Class 3 solvents are likely to be present. Loss on drying is not more than 0.5%.

(ii) Only Class 2 solvents are likely to be present. Name the Class 2 solvents that are present. All are not more than the Option 1 limit.

(iii) Only Class 2 solvents and Class 3 solvents are likely to be present. Residual Class 2 solvents are not more than the Option 1 limit and residual Class 3 solvents are not more than 0.5%.

If Class 1 solvents are likely to be present, they should be identified and quantified. ''Likely to be present'' refers to the solvents that were used in the final manufacturing step and to the solvents that were used in earlier manufacturing steps and not always possible to be excluded even in a validated process.

If solvents of Class 2 or Class 3 are present at greater than their Option 1 limits or 0.5%, respectively, they should be identified and quantified.

5. Limits of residual solvents

5.1. Solvents to be avoided in manufacture of pharmaceuticals

Solvents in Class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 2.46-1, unless otherwise justified. 1,1,1-Trichloroethane is included in Table 2.46-1 because it is an environmental hazard. The stated limit of 1500 ppm shown in Table 2.46-1 is based on a review of the safety data.

Table 2.46-1 Class 1 solvents in drug products (solvents that should be avoided)

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

5.2. Solvents to be limited in pharmaceuticals

Solvents in Table 2.46-2 should be limited in drug products because of their inherent toxicity.

PDEs are given to the nearest 0.1 mg per day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

5.3. Solvents with low toxic potential

Solvents in Class 3 shown in Table 2.46-3 may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. The amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5% under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice.

5.4 Solvents for which no adequate toxicological data was found

The following solvents (Table 2.46-4) may also be of interest to manufacturers of drug substances, excipients, or drug products. However, no adequate toxicological data on

Table 2.46-2 Class 2 Solvents which residual amount should be limited in drug products

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene	0.7	70
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,*N*-Dimethylacetamide	10.9	1090
N,*N*-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	3.1	310
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methyl butyl ketone	0.5	50
Methylcyclohexane	11.8	1180
Methyl isobutyl ketone	45	4500
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene*	21.7	2170

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethylbenzene

Table 2.46-3 Class 3 solvents which should be limited by GMP or other quality-based requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
n-Butyl acetate	Methyl ethyl ketone
tert-Butyl methyl ether	2-Methyl-1-propanol
Dimethylsulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Diethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	Triethylamine

which to base a PDE was found. Manufacturers should supply justification for residual levels of these solvents in drug products.

Table 2.46-4 Solvents for which no adequate toxicological data was found

1,1-Diethoxypropane	Methyl isopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

II. Identification and quantification of residual solvents

Whenever possible, the substance under test needs to be dissolved to release the residual solvent. Because drug products, as well as active ingredients and excipients are treated, it may be acceptable that in some cases, some of the components of the formulation will not dissolve completely. In those cases, the drug product may first need to be pulverized into a fine powder so that any residual solvent that may be present can be released. This operation should be performed as fast as possible to prevent the loss of volatile solvents during the procedure.

In the operating conditions of gas chromatography and headspace described below, parameters to be set and their description may be different depending on the apparatus. When setting these conditions, it is necessary to change them according to the apparatus used, if it is confirmed that they meet the system suitability.

In addition to the reagents specified to be used for the test, those that meet the purpose of the test can be used.

1. Class 1 and Class 2 residual solvents

The following procedures are useful to identify and quantify residual solvents when the information regarding which solvents are likely to be present in the material is not available. When the information about the presence of specific residual solvents are available, it is not necessary to perform Procedure A and Procedure B, and only Procedure C or other appropriate procedure is needed to quantify the amount of residual solvents.

A flow chart for the identification of residual solvents and the application of limit and quantitative tests is shown in Fig. 2.46-1.

1.1. Water-soluble articles

1.1.1. Procedure A

The test is performed by gas chromatography <*2.02*> according to the following conditions.

Class 1 standard stock solution: Pipet 1 mL of Residual Solvents Class 1 RS, dissolve in about 9 mL of dimethylsulfoxide, and add water to make exactly 100 mL. Pipet 1 mL of this solution in a volumetric flask, previously filled with about 50 mL of water and add water to make exactly 100 mL. Pipet 10 mL of this solution in a volumetric flask, previously filled with about 50 mL of water and add water to make exactly 100 mL.

Class 1 standard solution: Pipet 1 mL of Class 1 standard stock solution in an appropriate head space vial containing exactly 5 mL of water, apply the stopper, cap, and mix.

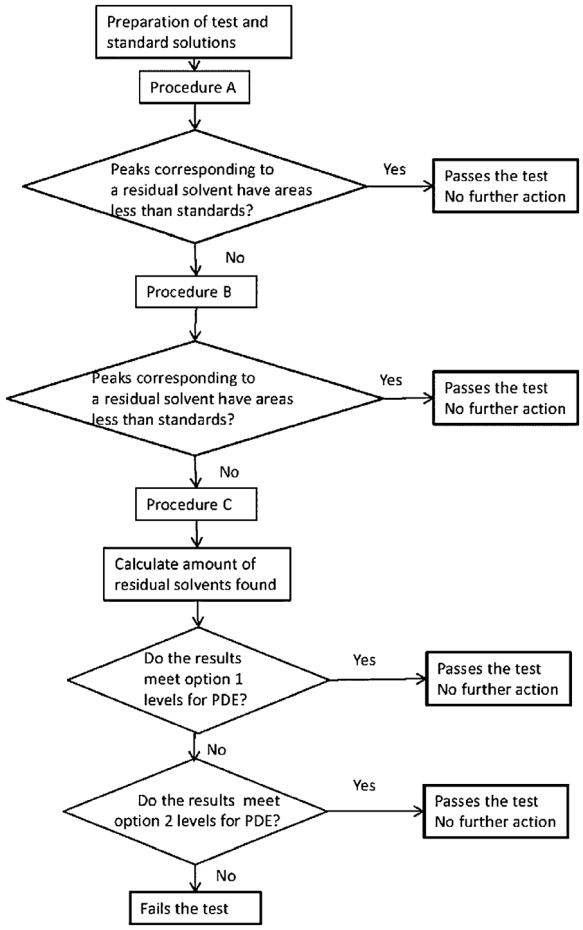


Fig. 2.46-1 Flow chart for the identification of residual solvents and the application of limit and qualification tests.

Class 2 standard stock solution A: Pipet 1 mL of Residual Solvents Class 2A RS, add water to make exactly 100 mL.

Class 2 standard stock solution B: Pipet 1 mL of Residual Solvents Class 2B RS, add water to make exactly 100 mL.

Class 2 standard stock solution C: Pipet 1 mL of Residual Solvents Class 2C RS, add water to make exactly 100 mL.

Class 2 standard solution A: Pipet 1 mL of Class 2 standard stock solution A in an appropriate headspace vial, add exactly 5 mL of water, apply the stopper, cap, and mix.

Class 2 standard solution B: Pipet 5 mL of Class 2 standard stock solution B in an appropriate headspace vial, add exactly 1 mL of water, apply the stopper, cap, and mix.

Class 2 standard solution C: Pipet 1 mL of Class 2 standard stock solution C in an appropriate headspace vial, add exactly 5 mL of water, apply the stopper, cap, and mix.

Test stock solution: Dissolve 0.25 g of the article under test in water, and add water to make exactly 25 mL.

Test solution: Pipet 5 mL of test stock solution in an appropriate headspace vial, add exactly 1 mL of water, and apply the stopper, cap, and mix.

Class 1 system suitability solution: Pipet 1 mL of Class 1 standard stock solution in an appropriate headspace vial, add exactly 5 mL of test stock solution, and apply the stopper, cap, and mix.

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A fused silica column (or a wide-bore column) 0.32 mm (or 0.53 mm) in inside diameter and 30 m in length, coated with 6% cyanopropylphenyl-94% dimethyl silicon polymer for gas chromatography in 1.8 μm (or 3.0 μm) thickness.

Column temperature: Maintain at 40°C for 20 minutes after injection, raise the temperature to 240°C at a rate of 10°C per minute, and maintain at 240°C for 20 minutes.

Injection port temperature: 140°C.

Detector temperature: 250°C.

Carrier gas: Nitrogen or Helium.

Flow rate: About 35 cm per second.

Split ratio: 1:5. (Note: The split ratio can be modified in order to optimize sensitivity.)

System suitability—

Test for required detectability: When the procedure is run with Class 1 standard solution and Class 1 system suitability solution under the above operating conditions, the SN ratio of the peak of 1,1,1-trichloroethane in Class 1 standard solution is not less than 5, and the SN ratio of each peak in Class 1 system suitability solution is not less than 3, respectively.

System performance: When the procedure is run with Class 2 standard solution A or the solution for system suitability under the above operating conditions, the resolution between acetonitrile and dichloromethane is not less than 1.0. Pipet 1 mL of a solution of Residual Solvents RS for System Suitability (1 in 100) in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix, and use this solution as the solution for system suitability.

System repeatability: When the test is repeated 6 times with Class 1 standard solution under the above operating conditions, the relative standard deviation of each peak area is not more than 15%.

Separately inject (following one of the headspace operating parameter sets described in Table 2.46-5) equal volumes of headspace (about 1.0 mL) of Class 1 standard solution, Class 2 standard solution A, Class 2 standard solution B, Class 2 standard solution C and test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak, other than a peak for 1,1,1-trichloroethane, in the test solution is greater than or equal to a corresponding peak in either Class 1 standard solution, Class 2 standard solution A, Class 2 standard solution B or Class 2 standard solution C, or a peak response of 1,1,1-trichloroethane is greater than or equal to 150 times the peak response corresponding to 1,1,1-trichloroethane in Class 1 standard solution, proceed to Procedure B to verify the identity of the peak; otherwise the article meets the requirements of this test.

1.1.2. Procedure B

The test is performed by gas chromatography <*2.02*> according to the following conditions.

Class 1 standard stock solution, Class 1 standard solution, Class 1 system suitability solution, Class 2 standard

stock solutions A, B and C, Class 2 standard solutions A, B and C, test stock solution and test solution: Prepare as directed for Procedure A.

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A fused silica column (or a wide-bore column) 0.32 mm (or 0.53 mm) in inside diameter and 30 m in length, coated with polyethylene glycol for gas chromatography in 0.25 μm thickness.

Column temperature: Maintain at 50°C for 20 minutes after injection, raise the temperature to 165°C at a rate of 6°C per minute, and maintain at 165°C for 20 minutes.

Injection port temperature: 140°C.

Detector temperature: 250°C.

Carrier gas: Nitrogen or Helium.

Flow rate: About 35 cm per second.

Split ratio: 1:5. (Note: The split ratio can be modified in order to optimize sensitivity.)

System suitability—

Test for required detectability: When the procedure is run with Class 1 standard solution and Class 1 system suitability solution under the above operating conditions, the SN ratio of the peak of benzene in Class 1 standard solution is not less than 5, and the SN ratio of each peak in Class 1 system suitability solution is not less than 3, respectively.

System performance: When the procedure is run with Class 2 standard solution A or the solution for system suitability under the above operating conditions, the resolution between acetonitrile and *cis*-1,2-dichloroethene is not less than 1.0. Pipet 1 mL of a solution of Residual Solvents RS for System Suitability (1 in 100) in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix, and use this solution as the solution for system suitability.

System repeatability: When the test is repeated 6 times with Class 1 standard solution under the above operating conditions, the relative standard deviation of each peak area is not more than 15%.

Separately inject (following one of the headspace operating parameter sets described in Table 2.46-5) equal volumes of headspace (about 1.0 mL) of Class 1 standard solution, Class 2 standard solution A, Class 2 standard solution B, Class 2 standard solution C and test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the test solution of the peak(s) identified in Procedure A is/are greater than or equal to a corresponding peak(s) in either Class 1 standard solution, Class 2 standard solution A, Class 2 standard solution B or Class 2 standard solution C, proceed to Procedure C to quantify the peak(s); otherwise the article meets the requirements of this test.

1.1.3. Procedure C

The test is performed by gas chromatography <*2.02*> according to the following conditions.

Class 1 standard stock solution, Class 1 standard solution, Class 2 standard stock solution A, Class 2 standard solution A, Class 2 standard stock solution C, Class 2 standard solution C and Class 1 system suitability solution: Prepare as directed for Procedure A.

Standard stock solution (Note: Prepare a separate standard stock solution for each peak identified and verified by Procedures A and B. For Class 1 solvents other than 1,1,1-trichloroethane, prepare the first dilution as directed for the first dilution under Class 1 standard stock solution in Procedure A.): Transfer an accurately measured volume of each individual solvent corresponding to each residual solvent peak identified and verified by Procedures A and B to a suitable container, and dilute quantitatively and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in Table 2.46-1 or Table 2.46-2.

Standard solution: Pipet 1 mL of standard stock solution in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix.

Test stock solution: Weigh accurately about 0.25 g of the article under test, dissolve in water, and add water to make exactly 25 mL.

Test solution: Pipet 5 mL of test stock solution in an appropriate headspace vial, add exactly 1 mL of water, and apply the stopper, cap, and mix.

Spiked test solution (Note: prepare a separate spiked test solution for each peak identified and verified by Procedure A and B): Pipet 5 mL of test stock solution in an appropriate headspace vial, add exactly 1 mL of standard stock solution, and apply the stopper, cap, and mix.

Operating conditions and system suitability fundamentally follow the procedure A. Test for required detectability is unnecessary, and use Standard solution instead of Class 1 standard solution for system repeatability. If the results of the chromatography from Procedure A are found to be inferior to those found with Procedure B, the operating conditions from Procedure B may be substituted.

Separately inject (following one of the headspace operating parameters described in Table 2.46-5) equal volumes of headspace (about 1.0 mL) of the standard solution, test solution, and spiked test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of each residual solvent found in the article under test by the formula:

$$\text{Residual solvent (ppm)} = 5\,(C/M)\{A_T/(A_S - A_T)\}$$

C: Concentration (μg/mL) of the appropriate Reference Standard in the standard stock solution

M: Amount (g) of the article under test taken to prepare the test stock solution

A_T: Peak responses of each residual solvent obtained from the test solution

A_S: Peak responses of each residual solvent obtained from the spiked test solution

1.2. Water-insoluble articles

1.2.1. Procedure A

The test is performed by gas chromatography <*2.02*> according to the following conditions. Dimethylsulfoxide may be substituted as an alternative solvent to *N*,*N*-dimethylformamide.

Class 1 standard stock solution: Pipet 1 mL of Residual Solvents Class 1 RS, dissolve in about 80 mL of *N*,*N*-dimethylformamide, and add *N*,*N*-dimethylformamide to make exactly 100 mL. Pipet 1 mL of this solution in a volumetric flask, previously filled with about 80 mL of *N*,*N*-dimethylformamide and add *N*,*N*-dimethylformamide to make exactly 100 mL (this solution is the intermediate dilution prepared from Residual Solvents Class 1 RS and use it for preparation of Class 1 system suitability solution). Pipet 1 mL of this solution, and add *N*,*N*-dimethylformamide to make exactly 10 mL.

Class 1 standard solution: Pipet 1 mL of Class 1 standard stock solution in an appropriate head space vial containing exactly 5 mL of water, apply the stopper, cap, and mix.

Class 2 standard stock solution A: Pipet 1 mL of Residual Solvents Class 2A RS, dissolve in about 80 mL of *N*,*N*-dimethylformamide, and add *N*,*N*-dimethylformamide to make exactly 100 mL.

Class 2 standard stock solution B: Pipet 0.5 mL of Residual Solvents Class 2B RS, add *N*,*N*-dimethylformamide to make exactly 10 mL.

Class 2 standard stock solution C: Pipet 1 mL of Residual Solvents Class 2C RS, dissolve in about 80 mL of *N*,*N*-dimethylformamide, and add *N*,*N*-dimethylformamide to make exactly 100 mL.

Class 2 standard solution A: Pipet 1 mL of Class 2 standard stock solution A in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix.

Class 2 standard solution B: Pipet 1 mL of Class 2 standard stock solution B in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix.

Class 2 standard solution C: Pipet 1 mL of Class 2 standard stock solution C in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix.

Test stock solution: Dissolve 0.5 g of the article under test in *N*,*N*-dimethylformamide, and add *N*,*N*-dimethylformamide to make exactly 10 mL.

Test solution: Pipet 1 mL of test stock solution in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix.

Class 1 system suitability solution: Pipet 5 mL of test stock solution and 0.5 mL of the intermediate dilution prepared from Residual Solvents Class 1 RS, and mix. Pipet 1 mL of this solution in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix.

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A wide-bore column 0.53 mm in inside diameter and 30 m in length, coated with 6% cyanopropylphenyl-94% dimethyl silicon polymer for gas chromatography in 3.0 μm thickness.

Column temperature: Maintain at 40°C for 20 minutes after injection, raise the temperature to 240°C at a rate of 10°C per minute, and maintain at 240°C for 20 minutes.

Injection port temperature: 140°C.

Detector temperature: 250°C.

Carrier gas: Helium.

Flow rate: About 35 cm per second.

Split ratio: 1:3. (Note: The split ratio can be modified in order to optimize sensitivity.)

System suitability—

Test for required detectability: When the procedure is run with Class 1 standard solution and Class 1 system suitability solution under the above operating conditions, the SN ratio of the peak of 1,1,1-trichloroethane in Class 1 standard solution is not less than 5, and the SN ratio of each peak in Class 1 system suitability solution is not less than 3, respectively.

System performance: When the procedure is run with Class 2 standard solution A or the solution for system suitability under the above operating conditions, the resolution between acetonitrile and dichloromethane is not less than 1.0. Pipet 1 mL of the *N*,*N*-dimethylformamide solution of Residual Solvents RS for System Suitability (1 in 100) in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix, and use this solution as the solution for system suitability.

System repeatability: When the test is repeated 6 times with Class 1 standard solution under the above operating conditions, the relative standard deviation of each peak areas is not more than 15%.

Separately inject (use headspace operating parameters in column 3 of Table 2.46-5) equal volumes of headspace (about 1.0 mL) of Class 1 standard solution, Class 2 standard solution A, Class 2 standard solution B, Class 2 standard solution C, and test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak, other than a peak for 1,1,1-trichloroethane, in the test solution is greater than or equal to a corresponding peak in either Class 1 standard solution, Class 2 standard solution A, Class 2 standard solution B or Class 2 standard solution C, or a peak response of 1,1,1-trichloroethane is greater than or equal to 150 times the peak response corresponding to 1,1,1-trichloroethane in Class 1 standard solution, proceed to Procedure B to verify the identity of the peak; otherwise, the article meets the requirements of this test.

1.2.2. Procedure B

The test is performed by gas chromatography <*2.02*> according to the following conditions.

Class 1 standard stock solution, Class 1 standard solution, Class 1 system suitability solution, Class 2 standard stock solutions A, B and C, Class 2 standard solutions A, B and C, test stock solution, and test solution: Proceed as directed for Procedure A.

Proceed as directed for Procedure B under Water-soluble articles with a split ratio of 1:3. (Note: The split ratio can be modified in order to optimize sensitivity.) The solution for system suitability: Proceed as directed for Procedure A.

Separately inject (use headspace operating parameters in Table 2.46-5) equal volumes of headspace (about 1.0 mL) of Class 1 standard solution, Class 2 standard solution A, Class 2 standard solution B, Class 2 standard solution C and test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in test solution of the peak(s) identi-

fied in Procedure A is/are greater than or equal to a corresponding peak(s) in either Class 1 standard solution, Class 2 standard solution A, Class 2 standard solution B or Class 2 standard solution C, proceed to Procedure C to quantify the peak; otherwise, the article meets the requirements of this test.

1.2.3 Procedure C

The test is performed by gas chromatography <2.02> according to the following conditions.

Class 1 standard stock solution, Class 1 standard solution, Class 1 system suitability solution, Class 2 standard stock solution A, Class 2 standard solution A, Class 2 standard stock solution C and Class 2 standard solution C: Proceed as directed for Procedure A.

Standard stock solution (Note: Prepare a separate standard stock solution for each peak identified and verified by Procedures A and B. For Class 1 solvents other than 1,1,1-trichloroethane, prepare the first dilution as directed for the first dilution under Class 1 standard stock solution in Procedure A.): Transfer an accurately measured volume of each individual solvent corresponding to each residual solvent peak identified and verified by Procedures A and B to a suitable container, and dilute quantitatively and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in Table 2.46-1 or Table 2.46-2.

Standard solution: Pipet 1 mL of standard stock solution in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix.

Test stock solution: Weigh accurately about 0.5 g of the article under test, and add *N*,*N*-dimethylformamide to make exactly 10 mL.

Test solution: Pipet 1 mL of test stock solution in an appropriate headspace vial, add exactly 5 mL of water, and apply the stopper, cap, and mix.

Spiked test solution (Note: prepare a separate spiked test solution for each peak identified and verified by Procedure A and B): Pipet 1 mL of test stock solution in an appropriate headspace vial, add exactly 4 mL of water, and apply the stopper, cap, and mix.

Operating conditions and system suitability fundamentally follow the procedure A. Test for required detectability is unnecessary, and use Standard solution instead of Class 1 standard solution for system repeatability. If the results of the chromatography from Procedure A are found to be inferior to those found with Procedure B, the operating conditions from Procedure B may be substituted.

Separately inject (use headspace operating parameters in Table 2.46-5) equal volumes of headspace (about 1.0 mL) of the standard solution, test solution, and spiked test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of each residual solvent found in the article under test by the formula:

$$\text{Residual solvent (ppm)} = 10\,(C/M)\{A_T/(A_S - A_T)\}$$

C: Concentration (μg/mL) of the appropriate Reference Standard in the standard stock solution

Table 2.46-5 Headspace operating parameters

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°C)	80	105	80
Equilibration time (min.)	60	45	45
Transfer-line temperature (°C)	85	110	105
Syringe temperature (°C)	80 – 90	105 – 115	80 – 90
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time (s)	≧ 60	≧ 60	≧ 60
Injection volume (mL)*	1	1	1

* Or follow the instrument manufacture's recommendations, as long as the method criteria are met. Injecting less than this amount is allowed as long as adequate sensitivity is achieved.

M: Amount (g) of the article under test taken to prepare the test stock solution

A_T: Peak responses of each residual solvent obtained from the test solution

A_S: Peak responses of each residual solvent obtained from the spiked test solution

1.3. Headspace operating parameters and other considerations

Examples of headspace operating parameters are shown in Table 2.46-5.

These test methods describe the analytical methods using the headspace gas chromatography. The following Class 2 residual solvents are not readily detected by the headspace injection conditions: 2-ethoxyethanol, ethylene glycol, formamide, 2-methoxyethanol, *N*-methylpyrrolidone, and sulfolane. Other appropriate validated procedures are to be employed for the quantification of these residual solvents. In the headspace methods, *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetoamide are often used as solvents. As not only 6 solvents described above but these two solvents are not included in the Residual Solvents Class 2A RS, the Residual Solvents Class 2B RS and/or the Residual Solvents Class 2C RS, appropriate validated procedures are to be employed for these residual solvents as necessary.

2. Class 3 residual solvents

Perform the test according to 1. Otherwise an appropriate validated procedure is to be employed. Prepare appropriately standard solutions, etc. according to the residual solvent under test.

If only Class 3 solvents are present, the level of residual solvents may be determined by Loss on Drying <2.41>. However when the value of the loss on drying is more than 0.5%, or other solvents exist, the individual Class 3 residual solvent or solvents present in the article under test should be identified using the procedures as described above or other appropriate procedure, and quantified as necessary.

3. Reference Standards

(i) Residual Solvents Class 1 RS (A mixture of benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene and 1,1,1-trichloroethane)

(ii) Residual Solvents Class 2A RS (A mixture of acetonitrile, chlorobenzene, cumene, cyclohexane, 1,2-dichloroethene (*cis*-1,2-dichloroethene, *trans*-1,2-dichloroethene), dichloromethane, 1,4-dioxane, methanol, methylcyclohexane, tetrahydrofuran, toluene and xylene (*m*-xylene, *p*-xylene, *o*-xylene, ethylbenzene))

(iii) Residual Solvents Class 2B RS (A mixture of chloroform, 1,2-dimethoxyethane, hexane, methyl butyl ketone, nitromethane, pyridine, tetralin and 1,1,2-trichloroethene)

(iv) Residual Solvents Class 2C RS (Methyl isobutyl ketone)

(v) Residual Solvents RS for System Suitability (A mixture of acetonitrile, *cis*-1,2-dichloroethene and dichloromethane)

2.51 Conductivity Measurement

Change the following as follows:

This test is harmonized with the European Pharmacopoeia and the U. S. Pharmacopeia.

The parts of the text that are not harmonized among the targeted texts for the harmonization are marked with symbols (◆ ◆), and the texts that are uniquely specified by the JP other than the targeted texts for the harmonization are marked with symbols (◇ ◇).

This chapter provides information on how to apply electrical conductivity measurements (hereafter referred to as ''conductivity'') of fluid solutions, including pure fluids. This chapter is intended for fluid applications when conductivity is used to measure, monitor, or control chemical dispensing, chemical purity, ionic concentration, and other applications where the ionic character of the fluid needs to be known or controlled.

Applications include, but are not limited to, solutions that may be used in clean-in-place, chromatography detection, ionic solution preparations, end point detection, dosing, fermentation, and buffer production. In some cases, conductivity measurements can be extended to pure organic fluids such as alcohols and glycols where a weak conductivity signal exists, and the signal can be significantly increased if the organics become contaminated with water or salts.

Conductivity is the measurement of the ability of a fluid to conduct electricity via its chemical ions. The ability of any ion to electrically conduct is directly related to its ion mobility. Conductivity is directly proportional to the concentrations of ions in the fluid, according to Equation (1):

$$\kappa = 100 \sum_{i}^{\substack{all\\ions}} C_i \cdot \lambda_i \qquad (1)$$

κ = conductivity (S/cm)
C_i = concentration of chemical ion i (mol/L)
λ_i = specific molar conductance of ion i (S·cm^2/mol)

Although the SI unit S/m is the appropriate SI unit for conductivity, historically the unit S/cm has been selected by industry as the accepted unit.

On the basis of Equation (1), conductivity is not ion selective because it responds to all ions. Furthermore, the specific molar conductance of each ion is different. As a result, unless the percentage composition of ions of the solution is limited and known, the precise concentrations of ionic species cannot be determined from conductivity measurements. However, for examples such as a solution of a single salt or acid or base, such as a caustic solution used in cleaning, the precise concentration can be directly determined. Despite the lack of ionic specificity, conductivity is a valuable laboratory and process tool for measurement and control of total ionic content because it is proportional to the sum of the concentrations of all ionic species (anions and cations) for diluted solutions as described in Equation (1). At higher concentrations, conductivity measurements are not perfectly linear with concentration. Conductivity measurements cannot be applied to solids or gases, but they can be applied to the condensate of gases.

Another variable that influences conductivity measurements is the fluid temperature. As the fluid temperature increases, the ion conductance increases, making this physicochemical phenomenon the predominant reason for the temperature-compensation requirement when testing conductive fluids.

The conductivity, κ, is proportional to the conductance, G (S), of a fluid between two electrodes (Equation (2)):

$$\kappa = G \times (d/A) = G \times K \qquad (2)$$

κ = conductivity (S/cm)
G = conductance (S)
d = distance between the electrodes (cm)
A = area of the conducting electrodes (cm^2)
K = cell constant (cm^{-1}), which also equals the ratio of d/A

The resistivity ρ (Ω·cm) of the fluid is, by definition, the reciprocal of the conductivity (Equation (3)):

$$\rho = 1/\kappa = 1/(G \times K) = R/K \qquad (3)$$

ρ = resistivity (Ω·cm)
κ = conductivity (S/cm)
G = conductance (S)
K = cell constant (cm^{-1})
R = resistance (Ω), which is the reciprocal of the conductance, G

1. Apparatus

An electrical conductivity measurement consists of the determination of resistance of the fluid between and around the electrodes of the conductivity sensor. To achieve this measurement, the primary instrumentation is the resistance-measuring circuit and the conductivity sensor, and they are

usually connected by a cable when the sensor and the user interface are separated.

The resistance measurement is made by applying an alternating current (AC, meaning the flow of electric charge periodically reverses direction) voltage (or current) to the electrodes, measuring the current (or voltage), and calculating the resistance according to Ohm's Law. The alternating source is used to prevent the polarization (collection of ions) at the electrodes. Depending on the instrument, the measuring frequency of the measuring system adjusts automatically according to the measuring conditions of the instrument, and there may be multiple resistance-measuring circuits embedded in the measuring system. The resistance-measurement circuit may be embedded in the transmitter or in the sensor.

The conductivity sensor consists of at least two electrical conductors of a fixed size and geometry, separated by an electrical insulator. The electrodes, insulator, and any other wetted materials should be constructed of materials that are unreactive to fluids with which they may come into contact. Also, the sensor construction should withstand the environmental conditions (process or ambient temperature, pressure, cleaning applications) that it would be subjected to.

Most conductivity sensors have temperature devices such as a platinum resistance temperature device (RTD) or negative temperature coefficient (NTC) thermistor embedded inside the sensor, although external temperature measurement is possible. The purpose of the temperature measurement is for temperature compensation of the conductivity measurement.

2. Cell Constant Determination

The purpose of the sensor's cell constant is to normalize the conductance (or resistance) measurement for the geometrical construction of the two electrodes.

The cell constant is determined by immersing the conductivity sensor in a solution of known conductivity. Solutions of known conductivity can be obtained by preparation of specific mixtures according to national authoritative sources or procurement of commercially available certified and traceable standard solutions. These recipes or certified solutions can range from 5 to 200,000 μS/cm, depending on the level of accuracy desired. Alternatively the cell constant is determined by comparison to other reference conductivity measuring systems (also available as an accredited calibration service). [Note—Conductivity measurements are not perfectly linear with concentration.]

The measured cell constant of the conductivity sensor must be within 5% of the nominal value indicated by the sensor certificate, unless otherwise prescribed.

Modern conductivity sensors normally do not change their cell constant over their lifetime. If a change of the cell constant is detected during calibration, a cleaning of the sensor is appropriate according to the manufacturer's recommendations. Following that, the calibration procedure should be repeated. Sometimes ''memory effects'' appear, particularly when changing from high to low concentrations if the sensor is not well flushed.

3. Calibration of Temperature

In addition to verifying the sensor's cell constant, the embedded temperature device (or external temperature device) should be appropriately calibrated for the application to apply the temperature compensation algorithm accurately. The temperature accuracy that is required depends on the criticality of the temperature to the application. An accuracy of ± 1°C typically suffices.

4. Calibration of Measurement Electronics

The measurement circuit of the system is fundamentally an AC resistance measuring device. Appropriate verification and/or calibration of the measuring circuit is required for measurement systems with signal transfer via analog cable. This is accomplished by disconnecting the measuring circuit from the sensor's electrodes, attaching traceable resistors of known value with the cable of the measurement system to the measuring circuit, and verifying that the measured resistance agrees with the resistor value to an acceptable level. A typical acceptance criterion for the resistance accuracy is $<2\%$ of the reading at resistances $>100\ \Omega$, and increasing to 5% at lower resistances. However, the application criticality should ultimately determine the desired accuracy.

For conductivity systems that cannot have the resistance-measuring circuit disconnected from the electrodes (e.g., measurement circuit and electrodes in one mutual housing), it may be difficult to directly adjust or verify the circuit accuracy, depending on the sensor design. An alternative method of verifying the measurement system integrity is a system calibration according to the procedures for the cell constant determination for each measuring circuit that is intended to be used.

If verification/calibration of the sensor's cell constant, temperature device, and measuring circuit are done at the same service interval, the measuring circuit should be verified first, the temperature device next, and the cell constant last. Because all of these parameters are typically very stable due to modern electronics and stable sensor construction, frequent calibration (such as daily) is not usually required. Comparison to qualified reference systems is also a proper means of calibration. Calibration is performed at appropriate intervals as defined in the quality management system.

5. Temperature Compensation

Because the conductivity of a fluid is temperature dependent, temperature compensation of the conductivity measurement is necessary unless otherwise prescribed. An appropriate temperature compensation algorithm will ensure that changes in the conductivity measurement can be ascribed to concentration changes and not temperature changes. Conductivity measurements are normally referenced to 25°C. A common form of linear temperature compensation uses Equation (4):

$$\kappa_{25} = \frac{\kappa_T}{[1 + \alpha(T - 25)]} \qquad (4)$$

κ_{25} = conductivity compensated to 25°C
κ_T = conductivity at T
α = temperature coefficient of the conductivity

T = measured temperature

A temperature coefficient of 2.1% per 1°C is commonly used for many salt solutions. Most salt-based solutions have linear compensation factors ranging from 1.9% to 2.2% per 1°C. Depending on the fluid samples, other forms of temperature compensation may be appropriate. ◇Non-linear temperature compensation will carry out temperature compensation using preprogrammed data in the instrument. Non-linear temperature compensation data for a variety of solutions is widely available, e.g. for natural waters, and for ultrapure water with traces of ammonia.◇ In cases of very low conductivity ($<10\ \mu$S/cm), such as purified pharmaceutical waters, two compensations need to be made. One is for the intrinsic conductivity of water, and the other is for the other ionic species in water. These compensations are normally combined and embedded in the microprocessor-controlled conductivity measurement systems. This is not supplied in all conductivity measurement technologies.

6. Conductivity Measurement of Fluids

For off-line batch measurements, rinse the cleaned sensor with the fluid to be measured. Then immerse the sensor in the fluid to be measured, and record the temperature and the temperature-compensated conductivity as required. Be sure that the position of the sensor in the container does not affect the conductivity measurement, because the container walls can affect the measurement for some electrode designs.

For continuous on-line or ◇in-line◇ measurements, install the cleaned sensor into the pipe, tank, or other containment vessel, and flush, if necessary. Make sure proper installation procedures are applied to prevent bubbles or particles from collecting between the electrodes. Be sure that the position of the sensor in the pipe or tank does not affect the conductivity measurement, because the nearby surfaces can affect the measurement for some electrode designs.

Record the temperature and the temperature-compensated conductivity as required.

For all batch or continuous measurements, ensure that the wetted components of the sensor are compatible with the fluid and the temperature to be measured.

Add the following:

2.66 Elemental Impurities—Procedures

Procedures of Elemental Impurities are methods to control elemental impurities contained in drug products and their components, etc. This chapter describes two analytical procedures (Procedures 1 and 2) and validation criteria for the evaluation of the levels of elemental impurities. The chapter permits the use of any procedure that meets the validation criteria specified in this chapter. As the chemical composition of the considered substances and the specification limits for the element(s) of interest vary considerably, it is difficult to describe all suitable sample preparation and measurement methods. By means of validation studies, analysts will confirm that the analytical procedure is suitable for use on specified material. It is not necessary to cross validate against either procedure 1 or 2 provided that requirements for procedure validation are met. As elemental impurities may be ubiquitous they have the potential to be present in trace amounts therefore special precautions may be necessary to avoid sample contamination. (Note: Methods such as atomic absorption spectrometry other than methods described in this chapter, if validated, can also be used without cross validation against analytical procedure 1 or 2.)

1. Sample Preparation

Forms of sample preparation include Neat, Direct aqueous solution, Direct organic solution, and Indirect solution. The selection of the appropriate sample preparation depends on the material under test and is the responsibility of the analyst. When a sample preparation is not indicated in the monograph, an analyst may use any appropriately validated sample preparation procedure, including but not limited to procedures described below. In cases where spiking of a material under test is necessary to provide an acceptable signal intensity, the blank should be spiked with the same Target elements, and where possible, using the same spiking solution. The material or mixture under test must be spiked before any sample preparation steps are performed. Standard solutions may contain multiple Target elements. (Note: If intended for a quantitative test, appropriate material handling procedures should be followed e.g. volatile liquids should be pipetted, viscous liquids should be weighed.)

Neat: Used for liquids or samples measurable without addition of solvent.

Direct aqueous solution: Used when the sample is soluble in an aqueous solvent.

Direct organic solution: Used when the sample is soluble in an organic solvent.

Indirect solution: Generally, an indirect solution is obtained when a material is not directly soluble in aqueous or organic solvents. Total metal extraction is the preferred sample preparation approach to obtain an indirect solution. Digest the sample using the Closed vessel digestion procedure provided below or one similar to it.

Closed vessel digestion: This sample preparation procedure is designed for samples that must be digested in a Concentrated acid using a closed vessel digestion apparatus. Closed vessel digestion minimizes the loss of volatile impurities. The choice of a Concentrated acid depends on the sample matrix. The use of any of the Concentrated acids may be appropriate, but each introduces inherent safety risks. Therefore, appropriate safety precautions should be used at all times. (Note: Weights and volumes provided may be adjusted to meet the requirements of the digestion apparatus used.)

An example procedure that has been shown to have broad applicability is the following. Dehydrate and predigest 0.5 g

of material under test in 5 mL of freshly prepared Concentrated acid. Allow to sit loosely covered for 30 minutes in a fume hood. Add an additional 10 mL of Concentrated acid, and digest, using a closed vessel technique, until digestion or extraction is complete. Repeat, if necessary, by adding an additional 5 mL of Concentrated acid. (Note: Where closed vessel digestion is necessary, follow the manufacturer's recommended procedures to ensure safe use.)

Clear solutions are expected in the validation. In those cases where a clear solution cannot be obtained, appropriate studies should ensure that the recovery is suitable for the intended use.

Reagents: All reagents used for the preparation of sample and standard solutions should be sufficiently pure for the intended purpose.

2. Analytical Procedures 1 and 2

System standardization and suitability evaluation using applicable reference materials should be performed for each analytical sequence.

2.1. Procedure and Detection Technique

Procedure 1 can be used for elemental impurities generally amenable to detection by inductively coupled plasma-atomic (optical) emission spectroscopy (ICP – AES or ICP – OES). Procedure 2 can be used for elemental impurities generally amenable to detection by inductively coupled plasma-mass spectrometry (ICP – MS). Before initial use, the analyst should verify that the procedure is appropriate for the instrument and sample used by meeting the procedure validation requirements below.

2.2. Procedure 1: ICP – OES

Standard solution 1: 1.5*J* of the Target element(s) in a Matrix matched solution

Standard solution 2: 0.5*J* of the Target element(s) in a Matrix matched solution

Sample stock solution: Proceed as directed in Sample Preparation above. Allow the sample to cool, if necessary. For mercury determination, add an appropriate stabilizer, if necessary.

Sample solution: Dilute the Sample stock solution with an appropriate solvent to obtain a final concentration of the Target element(s) within the calibrated range.

Blank: Matrix matched solution

Elemental spectrometric system

Mode: ICP

Detector: Optical detection system

Rinse: Generally, diluent used

Calibration: Standard solution 1, Standard solution 2, and Blank

System suitability Sample: Standard solution of the Target element(s) in a Matrix matched solution at a concentration within the calibrated range

Suitability requirements

Short term Instrumental Stability: Compare results obtained from System suitability sample before and after the analysis of the Sample solution.

Suitability criteria: NMT 20% deviation between both samples for each Target element. (Note: If samples are high in mineral content, rinse the system well in order to minimize carryover and check it by measuring a blank solution before introducing the System Suitability Sample.)

Analysis: Analyze according to manufacture's suggestions for wavelength. Calculate and report results on the basis of the original sample size. [Note: Appropriate measures must be taken to correct for matrix-induced interferences (e.g., wavelength overlaps).]

2.3. Procedure 2: ICP – MS

Standard solution 1: 1.5*J* of the Target element(s) in a Matrix matched solution

Standard solution 2: 0.5*J* of the Target element(s) in a Matrix matched solution

Sample stock solution: Proceed as directed in Sample Preparation above. Allow the sample to cool, if necessary. For mercury determination, add an appropriate stabilizer, if necessary.

Sample solution: Dilute the Sample stock solution with an appropriate solvent to obtain a final concentration of the Target element(s) within the calibrated range.

Blank: Matrix matched solution

Elemental spectrometric system

Mode: ICP. [Note: An instrument with a cooled spray chamber is recommended. (A collision cell or reaction cell may also be beneficial.)]

Detector: Mass spectrometer

Rinse: Generally, diluent used

Calibration: Standard solution 1, Standard solution 2, and Blank

System suitability Sample: Standard solution of the Target element(s) in a Matrix matched solution at a concentration within the calibrated range

Suitability requirements

Short term Instrumental Stability: Compare results obtained from system suitability sample before and after the analysis of the Sample solution.

Suitability criteria: NMT 20% deviation between both samples for each Target element. (Note: If samples are high in mineral content, rinse the system well in order to minimize carryover and check it by measuring a blank before introducing the System suitability sample.)

Analysis: Analyze according to the manufacturer's suggestions for program and m/z. Calculate and report results based on the original sample size. [Note: Appropriate measures must be taken to correct for matrix-induced interferences (e.g., argon chloride interference with arsenic determinations).]

3. Requirements for Procedure Validation

All procedures must be validated and shown to be acceptable, in accordance with the validation requirements described below. The level of validation necessary to ensure that a procedure is acceptable depends on whether a limit test or a quantitative determination is used. Any procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use. If appropriate, the validation method and criteria may be changed according to the purpose of evaluating the levels of the con-

tent of elemental impurities. They may differ from the requirements to meet the system suitability criteria described in Inductively Coupled Plasma-Atomic Emission Spectrometry and Inductively Coupled Plasma-Mass Spectrometry <*2.63*>.

3.1. Procedures for Limits Tests

The following section defines the validation parameters for the acceptability of limit tests. Meeting these requirements must be demonstrated experimentally using an appropriate system suitability test and reference materials.

The suitability of the method must be determined by conducting studies with the material or mixture under test spiked with known concentrations of each Target element of interest at the appropriate Target concentration.

3.1.1. Detectability

Standard solution: A preparation of reference materials for the Target element(s) at 1.0*J* in a Matrix matched solution.

Spiked sample solution 1: Prepare a solution of the sample under test, spiked with appropriate reference materials for the Target element(s) at the Target concentration, solubilized or digested as described in Sample Preparation.

Spiked sample solution 2: Prepare a solution of the sample under test, spiked with appropriate reference materials for the Target element(s) at 80% of the Target concentration, solubilized or digested as described in Sample Preparation.

Unspiked sample solution: A sample of material under test, solubilized or digested in the same manner as the spiked Sample solutions

Acceptance criteria

Non-instrumental procedures: Spiked sample solution 1 provides a signal or intensity equivalent to or greater than that of the Standard solution. Spiked sample solution 2 must provide a signal or intensity less than that of Spiked sample solution 1. (Note: The signal from each Spiked sample solution is NLT the Unspiked sample solution determination.)

Instrumental procedures: The average value of the three replicate measurements of Spiked sample solution 1 is within ± 15% of the average value obtained for the replicate measurements of the Standard solution. The average value of the replicate measurements of Spiked sample solution 2 must provide a signal intensity or value less than that of the Standard solution. (Note: Correct the values obtained for each of the spiked solutions using the Unspiked sample solution.)

3.1.2. Specificity

The procedure must be able to unequivocally assess each Target element in the presence of components that may be expected to be present, including other Target elements, and matrix components.

3.1.3. Precision, only for Instrumental Methods (Repeatability)

Sample solutions: Six independent samples of the material under test, spiked with appropriate reference materials for the Target elements at the Target concentration

Acceptance criteria

Relative standard deviation: NMT 20% for each Target element

3.2. Procedures for Quantitative Tests

The following section defines the validation parameters for the acceptability of procedures for quantitative tests. Meeting these requirements must be demonstrated experimentally, using an appropriate system suitability test and reference materials.

3.2.1. Accuracy

Standard solutions: Prepare solutions containing the Target element(s) at three concentrations ranging from 0.5 to 1.5*J*, using appropriate reference materials, in a Matrix matched solution and blank.

Test samples: Prepare samples of the material under test spiked with appropriate reference materials for the Target element(s) before any sample preparation steps (digestion or solubilization) at 3 concentrations ranging from 50% to 150% of the Target concentration. Spike concentrations should range from 0.5 to 1.5*J*, and should contain at least three individual concentrations.

Acceptance criteria

Spike recovery: 70% – 150% for the mean of three replicate preparations at each concentration

3.2.2. Precision

Repeatability

Test samples: Six independent samples of material under test (taken from the same lot) spiked with appropriate reference materials for the Target element(s) at the Target concentration. Or at least 9 determinations (e.g., 3 replicates of 3 concentrations) covering the specified range.

Acceptance criteria

Relative standard deviation: NMT 20% (n = 6) for each Target element

Intermediate precision (ruggedness)

Perform the Repeatability analysis again at least once either on a different day, with a different instrumentation, with a different analyst, or a combination thereof. Combine the results of this analysis with the Repeatability analysis so the total number of samples is at least 12.

Acceptance criteria

Relative standard deviation: NMT 25% (n = 12) for each Target element

3.2.3. Specificity

The procedure must be able to unequivocally assess each Target element in the presence of components that may be expected to be present, including other Target elements, and matrix components.

3.2.4. Range and Linearity

Demonstrated by meeting the Accuracy requirement.

3.2.5. Limit of Quantification

The Limit of Quantification is confirmed when the accuracy acceptance criteria for the corresponding spiked solution is met. The Limit of Quantification is smaller or equal to 50% of Target concentration.

4. Glossary

(i) Concentrated acid: Concentrated ultra-pure nitric, sulfuric, hydrochloric, or hydrofluoric acids or any other acid or mixture of acids that is demonstrated suitable.

(ii) Matrix matched solution: Solutions having the same

solvent composition as the Sample solution. In the case of an aqueous solution, Matrix matched solution would indicate that the same acids, acid concentrations and mercury stabilizer are used in both preparations.

(iii) Target elements: Elements whose levels in the drug product must be controlled within acceptable limits.

(iv) Target limit or Target concentration: The acceptance value for the elemental impurity being evaluated. Exceeding the Target limit indicates that a material under test exceeds the acceptable value. Target limits in the final drug product can be approximated by dividing the permitted daily exposures (PDEs) by the maximum daily dose of the drug product. When evaluating the significance of elemental impurity levels, it is possible to set the Target limits to the values obtained by dividing 30% of PDEs by the maximum daily dose of the drug product. Furthermore, when the permitted concentration limit of each element in the individual components of the drug product is set, it can be set as the Target concentration.

(v) *J*: The concentration (w/v) of the Target element(s) at the Target limit, appropriately diluted to the working range of the instrument. If a dilution is not necessary, *J* is equal to the Target concentration. For example, if the target elements are lead and arsenic for an analysis of an oral solid drug product with a daily dose of 10 g/day using inductively coupled plasma – mass spectrometry (ICP – MS), the target limit for these elements would be 0.5 μg/g and 1.5 μg/g. However, in both cases, the linear dynamic range of the ICP – MS is known to extend from 0.01 ng/mL to 0.1 μg/mL for these elements. Therefore, a dilution factor of at least 1:100 is required to ensure that the analysis occurs in the linear dynamic range of the instrument. *J* would thus equal 5 ng/mL and 15 ng/mL for lead and arsenic, respectively.

(vi) Appropriate reference materials: In principle, where Appropriate reference materials are specified in the chapter, certified reference materials (CRM) from a national metrology institute (NMI), or reference materials that are traceable to the CRM of an NMI should be used.

(vii) Cross validation: Verification whether or not the same result can be obtained from the corresponding analyses for the same sample.

Add the following:

6.16 Rheological Measurements for Semi-solid Preparations

Rheological measurements for semi-solid preparations are methods to measure fluidity and deformation by adding force to semi-solid preparations such as Semi-solid Preparations for Oro-mucosal Application, Ophthalmic Ointments, Ointments, Creams and Gels.

There are two methods, the first (spreadability test) and the second (penetrometry).

These methods are more practical to determine rheological properties of semi-solid preparations, though Method II Viscosity measurement by rotational viscometer under Viscosity Determination <*2.53*> can evaluate precisely rheological properties of semi-solids.

1. Method 1 Spreadability test

Spreadability test is a method for measuring flowability of semi-solid preparations using a spread meter (also known as a parallel plate viscometer).

A spread meter measures a spreading diameter etc. of a sample by observing the characteristic of the concentric spreading over time when the sample is sandwiched between two parallel plates [glass (or plastic) plate and fixed plate] placed horizontally and pushed outward with the own weight of the glass plate.

Generally there is a reciprocal relationship between fluidity as an index of flowability and viscosity, however flowability measured by this method does not necessarily correlate with apparent viscosity (mPa·s) measured by the viscosity determination.

This method targets relatively soft preparations in particular among semi-solid preparations.

1.1. Apparatus

An example of spread meters is shown in Fig. 6.16-1.

There are two parallel plates placed horizontally. The fixed plate installed in the lower part has engraved scales at 1 mm intervals to measure the distance from the center and has a cylindrical hole (0.5 mL) at the center for inserting a sample. The weight-loading glass plate positioned in the upper part is made of transparent glass or acrylate resin etc. and has a mass of 115 g. The glass plate is supported by rods. Pushing the piston up raise the bottom of the hole to push the sample above the fixed plate. In connection with it the glass plate falls (20 mm, commonly) and the sample spreads concentrically on the fixed plate with the own weight of the glass plate. Measuring the extent of the spread provides the flowability of the sample.

1.2. Procedure and measurement conditions

Before measurement remove a glass plate from an apparatus and clean the glass plate, a fixed plate and a specimen hole. Fill a sample in the specimen hole at the center of the fixed plate and flatten the sample by a spatula etc. so that the upper face of the sample is flush with the fixed plate and become flat. Wipe the sample protruded off. Make sure that the apparatus is horizontal by a level and install the glass plate to the support rod. Push the piston up and start time measurement simultaneously. Measure the spread of the sample on the fixed plate by the scale in mm unit over time and record them.

A constant temperature is needed during measurement and it is preferable to perform the measurement in the room controlled at 25 ± 2°C.

Bring the temperature of samples equal to that of the measurement environment by allowing them to stand in the measurement environment.

1.3. Analysis

Characteristics of flowability obtained with the measurement using a spread meter are expressed as spread meter

diameter D and spread meter yield value YV in the case of the single-point method and as spread meter slope S and spread meter intercept IC in the case of the multi-point method. They are calculated by the following methods, respectively.

1.3.1. Single-point method

(i) Spread meter diameter *D:* Expressed as the spreading diameter (mm) after the specified time (usually, 60 seconds).

A larger spreading diameter indicates higher flowability.

(ii) Spread meter yield value *YV:* Calculate by the following equation.

$$YV = (4.8 \times W \times V \times g_n)/(\pi^2 \times D_\infty{}^5)$$

YV: Yield value (Pa)
W: Mass (kg) of glass plate
V: Sample volume (m^3)
g_n: Standard acceleration due to gravity (m/s^2)
D_∞: Maximum of spreading diameter (m)

The above equation is expressed in the International System of Units, however actual measurement is performed in the Centimeter-Gram-Second System of Units.

Many semi-solid preparations have no flowability when leave them as they are, however they flow by adding force. The limit value of the force is the yield value and a larger yield value indicates that a larger force is required for the flow of a sample.

1.3.2. Multi-point method

(i) Spread meter slope *S:* Calculate by the following equation.

$$S = (D_2 - D_1)/\log_{10}(T_2/T_1)$$

D_1: Spreading diameter after T_1 seconds (mm)
D_2: Spreading diameter after T_2 seconds (mm)
T_1, T_2: Measurement time (seconds) $T_2 > T_1$, $5 \leqq T_1$ and $T_2 \leqq 100$, $\Delta T = (T_2 - T_1) > 40$

In general, plot the spreading diameter measured each time on a semi-logarithmic graph to obtain an almost straight line connecting each point. Spread meter slope S corresponds to its slope.

A larger S indicates a larger flow of a sample.

(ii) Spread meter intercept *IC:* Plot logarithms of times (T_1, T_2) as abscissa against spreading diameters (D_1, D_2) as ordinate and draw a line connecting these two points. Obtain the intersection point ($T = 1$) of this extension line and the ordinate axis as spread meter IC.

A larger IC indicates higher flowability of a sample.

2. Method 2 Penetrometry

Penetrometry is a method for measuring hardness or softness of semi-solid preparations using a penetrometer.

A penetrometer is an apparatus for measuring the distance traveled by a cone penetrant inside a sample and the consistency is expressed as ten times of the value measured in units of 0.1 mm. A smaller value indicates a harder sample.

This method targets relatively hard preparations in particular among semi-solid preparations.

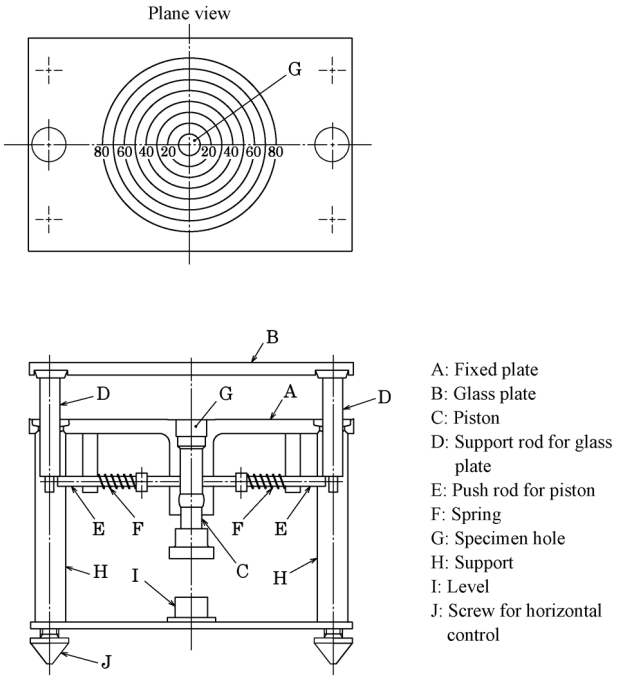


Fig. 6.16-1 Example of spread meter

2.1. Apparatus

2.1.1. Penetrometer

An example of penetrometers is shown in Fig. 6.16-2.

Adjust a penetrometer so that the position of the tip of a prescribed cone touches the surface of the sample filled in a sample container, penetrate the cone into the sample with its own weight for a certain time and calculate the consistency from the depth measured in units of 0.1 mm.

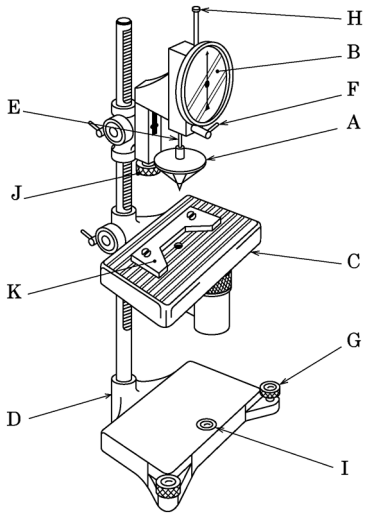
Adjust exactly the cone part or the sample stage of the penetrometer so that the position of the tip of the cone touches the horizontal surface of the sample keeping the reading of the dial gage zero. Adjust the cone in advance so that the cone falls more than 62 mm smoothly when released from the state fixed to the penetrometer and the top of the cone does not hit the bottom of the sample container after the fall. The penetrometer must be equipped with a screw for horizontal control and a level to maintain a cone holder being vertical.

2.1.2. Cone

A standard cone is a conical body made of magnesium or other suitable metal, which has a removable hardened steel needle. Fig. 6.16-3 shows the specifications of the standard cone.

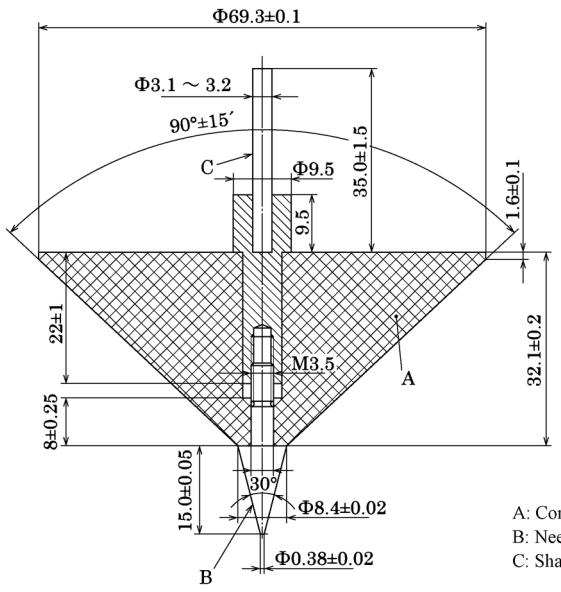
The upper end of a holder is equipped with a stopper and the lower end is devised to connect a cone. The inner structure of the cone may be changed in order to conform to the prescribed mass as far as there is no change in shape and mass distribution of the cone. The outer surface of the cone must be without scratches and smooth enough.

Fig. 6.16-4, 6.16-5 and 6.16-6 show the specifications of an optional cone, a half-scale cone and a quarter-scale cone. The half-scale and quarter-scale cones are the prescribed cones that are scaled down to a half and a quarter of the



A: Cone
B: Dial gage
C: Sample stage
D: Support base
E: Holder
F: Metal clamping tool
G: Screw for horizontal control
H: Rack for measurement
I: Level
J: Fine adjustment knob
K: Centering tool

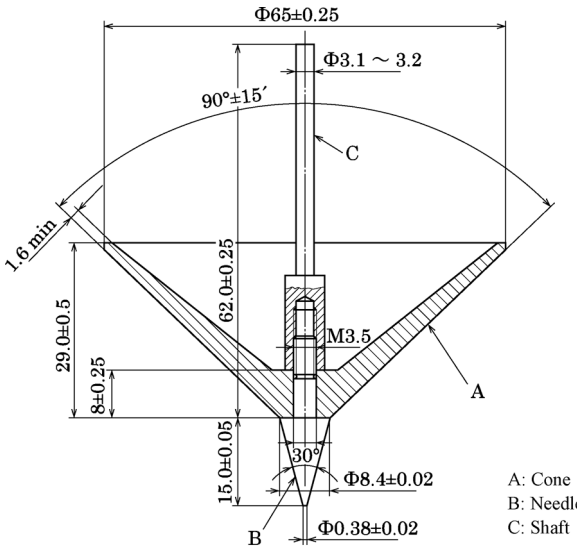
Fig. 6.16-2 Example of penetrometer



A: Cone
B: Needle tip
C: Shaft

Total mass of cone: 102.5±0.05 g
Total mass of holder: 47.5±0.05 g

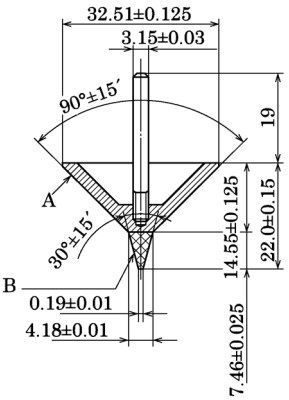
Fig. 6.16-3 Standard cone



A: Cone
B: Needle tip
C: Shaft

Total mass of cone: 102.5±0.05 g
Total mass of holder: 47.5±0.05 g

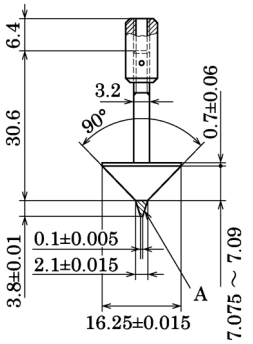
Fig. 6.16-4 Optional cone



A: Cone
B: Needle tip

Total mass of cone: 22.5±0.025 g
Total mass of holder: 15.0±0.025 g
Total mass of cone and holder: 37.5±0.050 g

Fig. 6.16-5 Half-scale cone



A: Needle tip

Total mass of cone and holder: 9.38±0.025 g

Fig. 6.16-6 Quarter-scale cone

standard cone or the optional cone.

Select a suitable cone based on the sample volume and the consistency of the preparation to be tested and convert the measured consistency to the value equivalent to that measured using a standard cone.

An optional cone may be used to measure the sample having a consistency of not more than 400. Use a half-scale cone or a quarter-scale cone, when a sample has a consistency of 175 to 385 and a standard cone is not available because of small sample amounts.

2.2. Procedure and measurement conditions

2.2.1. Sample preparation

Stand a prepared empty container and a container with a lid containing a necessary amount of sample in a water bath at 25°C and bring the temperature of the sample at 25 ± 0.5°C. Transfer the sample in the container with a lid to the empty container at a time, if possible. Remove air bubbles mixed in the sample in the sample container by a suitable method and fill the container with an excessive amount of the sample using a spatula again. Be careful not to stir the sample and not to make vacant space inside the sample in this procedure. Flatten the surface of the sample by removal of the excessive sample by moving a spatula, of which surface is inclined about 45 degrees in the direction of the movement, along the upper edge of the container. Hereafter do not touch the surface of the sample before measurement. Perform the test promptly to keep the temperature of the sample evenly at 25 ± 0.5°C.

The consistency of soft samples is affected by the container diameter. With soft samples having a consistency of not less than 265, use a container with inside diameter of 76.2 mm (a half-scale cone: 38.1 mm, a quarter-scale cone: 19.0 mm). The consistency of relatively hard samples having a consistency of not more than 265 is hardly affected by the container diameter when using a container with inside diameter of not less than 76.2 mm.

The amount of sample required for the test depends on the sizes of the sample container and the cone, and the procedure specified according to the cosistency.

2.2.2. Procedure

2.2.2.1. Standard cone

Stand a sample container gently on the sample stage of the penetrometer adjusted to horizontal position. After placing the position of the cone to the zero point of the dial gage adjust the cone so that the tip touches the surface of the sample at the position prescribed in (i), (ii) or (iii) by moving either the cone part or the sample stage up and down. Push the metal clamping tool immediately to penetrate the cone for 5 ± 0.1 seconds. The holder must move smoothly in the drop unit. Push the rack for measurement down gently until it stops and read the dial gage in first place after the decimal point.

(i) With a sample having a consistency of more than 400, only one test may be made in one container by placing the center of the sample container within 0.3 mm from the needle tip. Three tests may be made in three containers.

(ii) With a sample having a consistency of more than 200 and less than 400, perform carefully the centering of the cone in the sample container. Only one test may be made with this sample. Three tests may be made in three containers.

(iii) With a sample having a consistency of not more than 200, three tests may be made in one container. The measurement points are the midpoints between the center and the edge of the sample container at about 120 degrees intervals on a concentric circle.

2.2.2.2. Half-scale cone and quarter-scale cone

Place a cone at the center of a sample surface and perform a penetration pretest. The pretest may be omitted if an approximate value of consistency is known. Perform the measurement of consistency according to the procedure in 2.2.2.1. and place the position of the tip according to the following (i) or (ii).

(i) With a sample having a consistency of more than 97 when using a half-scale cone or more than 47 when using a quarter-scale cone, only one test may be made in one container by placing carefully the needle tip at the center of the sample container. Three tests may be made in three containers.

(ii) With a sample having a consistency of not more than 97 when using a half-scale cone or not more than 47 when using a quarter-scale cone, three tests may be made in one sample container. The measurement points are the midpoints between the center and the edge of the sample container at about 120 degrees intervals on a concentric circle so that the cone does not collide with the edge of the sample container and the measurement position of previous tests.

2.3. Analysis

2.3.1. Conversion of consistency measured using a half-scale or quarter-scale cone

Convert the consistency obtained using a half-scale or quarter-scale cone to the value equivalent to that obtained using a standard cone by the following equation.

2.3.1.1. Conversion of consistency obtained using a half-scale cone

$$P = 2p_{1/2} + 5$$

P: Consistency converted to the value equivalent to that measured using the standard cone

$p_{1/2}$: Consistency measured using a half-scale cone

2.3.1.2. Conversion of consistency obtained using a quarter -scale cone

$$P = 3.75p_{1/4} + 24$$

P: Consistency converted to the value equivalent to that measured using a standard cone

$p_{1/4}$: Consistency measured using a quarter-scale cone

Add the following:

6.17 Insoluble Particulate Matter Test for Therapeutic Protein Injections

Insoluble particulate matters in injections consist of mobile undissolved particles other than gas bubbles in preparations. Extraneous substances, substances derived from manufacturing processes, protein aggregates and so on may be included in therapeutic protein injections. In this chapter, Method 1 (Light Obscuration Particle Count Test) under Insoluble Particulate Matter Test for Injections <*6.07*> is used for the determination of insoluble particulates in therapeutic protein injections. This test is applied to the injections whose active ingredients are peptides, proteins or their derivatives.

Since this test is a sampling test conducted on a part of samples, the test must be performed under a statistically sound sampling plan in order to estimate correctly the number of particles in the population.

1. Apparatus

Use a suitable apparatus based on the principle of light blockage which allows an automatic determination of the size of particles and the number of particles according to size. Calibration, and verification of sample volume accuracy, sample flow rate accuracy and counting accuracy are performed according to Method 1 under Insoluble Particulate Matter Test for Injections <*6.07*>. When one measurement is performed with volume less than 1 mL, confirm the sample volume accuracy separately by an appropriate method.

2. General precautions

The test is carried out under conditions limiting particulate contamination, preferably in a laminar-flow cabinet. Very carefully wash the glassware and filtration equipment used, except for the membrane filters, with a warm detergent solution and rinse with abundant amounts of water to remove all traces of detergent. Immediately before use, rinse the equipment from top to bottom, outside and then inside, with *particle-free water*. Take care not to introduce air bubbles into the preparation to be examined, especially when fractions of the preparation are being transferred to the container in which the determination is to be carried out. In order to check that the environment is suitable for the test, that the glassware is properly cleaned and that the number of particles in the *particle-free water* to be used is within specifications, the following test is carried out using 5 mL of the *particle-free water*. When one measurement is performed with volume less than 1 mL, 1 mL of *particle-free water* may be used. Determine the particulate contamination of 5 samples of *particle-free water*. If the number of particles of 10 μm or greater size exceeds 1 per 1 mL, the precautions taken for the test are not sufficient. In this case, the preparatory steps must be repeated until the environment, filtration equipment glassware and *particle-free water* are suitable for the test.

3. Method

Treat a protein solution in an appropriate manner because of its tendency to generate air bubbles. In the case of an injection to be dissolved before use, use a specified solvent. When solvent is not specified, dissolve in *particle-free water* or use other suitable solvent comparable to *particle-free water*. Mix the appropriate contents of the sample gently and thoroughly by an appropriate procedure such as swirling the container slowly. If the container is sealed, cautiously remove the sealing closure. Clean the outer surfaces of the container opening using a jet of *particle-free water* and remove the closure, avoiding any contamination at the contents. For elimination of air bubbles, it is recommended to allow a container to stand under ambient pressure or reduced pressure. Other procedures are applicable if confirmed to be appropriate. Sonicating is not appropriate because it may aggregate or denature proteins. If necessary, after degassing, mix the contents gently and thoroughly by swirling slowly the container so as not to introduce air bubbles, and use it for the test. The measurement volume is 1 to 5 mL. The measurement volume can be reduced to 0.2 mL when the validity of the reduction is confirmed in considering the property of the sample and the tare volume of the apparatus. Set the volume necessary for the test in consideration of counting 4 portions.

In the case of injections where the volume necessary for the test can be obtained from one container, individual containers are tested. For injections with insufficient volume, combine the contents of several containers in one clean container to obtain the necessary volume after mixing the contents of containers gently and thoroughly. Where justified, the volume necessary for the test may be prepared by diluting the test solution with *particle-free water* or an appropriate solvent comparable to *particle-free water*. The validity of the dilution procedure and the solvent used for the dilution is confirmed by, for example, demonstrating consistent result regardless of the dilution. The number of test specimens must be adequate to provide a statistically sound assessment.

Take 4 portions and count the number of particles equal to or greater than 10 μm and 25 μm. Disregard the result obtained for the first portion, and calculate the mean number of particles for the preparation to be examined.

4. Evaluation

The preparation complies with the test if the average number of particles meets the following requirement.

A—Solutions for injection supplied in containers with a nominal content of equal to or more than 100 mL.

The average number of particles of equal to or greater than 10 μm does not exceed 25 per mL and that of particles of equal to or greater than 25 μm does not exceed 3 per mL.

B—Solutions for injection supplied in containers with a nominal content of less than 100 mL.

The average number of particles of equal to or greater than 10 μm does not exceed 6000 per container and that of particles of equal to or greater than 25 μm does not exceed

600 per container.

9.01 Reference Standards

Add the following to section (1):

Bromfenac Sodium RS
L-Carnosine RS
Doripenem RS
Gatifloxacin RS
Hydroxyethylcellulose RS for Identification
Lanoconazole RS
Microcrystalline Cellulose RS for Identification
Residual Solvents Class 2C RS
Sitagliptin Phosphate RS
Sitagliptin Phosphate RS for System Suitability

Move the following from section (2) to section (1):

Ampicillin RS
Azithromycin RS
Cefazolin RS
Cefmetazole RS
Fradiomycin Sulfate RS
Meropenem RS

9.21 Standard Solutions for Volumetric Analysis

Add the following:

Cerium (IV) Sulfate, 0.1 mol/L

1000 mL of this solution contains 40.43 g of cerium (IV) sulfate tetrahydrate [Ce $(SO_4)_2.4H_2O$: 404.30].

Preparation—Dissolve 40.43 g of cerium sulfate (IV) tetrahydrate in water to make 1000 mL, and standardize the solution as follows:

Standardization—Weigh accurately about 0.2 g of sodium oxalate (standard reagent), previously dried between 150°C and 200°C for 1 to 1.5 hours, and allow to cool in a desiccator (silica gel), and dissolve in 75 mL of water. Add a mixture of 5 mL of water and 2 mL of sulfuric acid with stirring, add 10 mL of hydrochloric acid, and warm to 70 – 75°C. Titrate <2.50> the solution with 0.1 mol/L cerium (IV) sulfate VS until the solution shows a persistent slightly yellow color, and calculate the molarity factor.

Each mL of 0.1 mol/L cerium sulfate (IV) VS
= 6.700 mg of $Na_2C_2O_4$

Iodine, 0.025 mol/L

1000 mL of this solution contains 6.345 g of iodine (I:126.90).

Preparation—Before use, dilute 0.05 mol/L iodine VS with water to make exactly twice the initial volume.

9.22 Standard Solutions

Add the following:

Standard Chloride Solution Pipet 10 mL of Standard Chloride Stock Solution, add water to make exactly 1000 mL. Prepare before use. Each mL of this solution contains 5 μg of chloride (Cl).

Standard Chloride Stock Solution Weigh accurately 0.842 g of sodium chloride, previously dried at 130°C for 2 hours, and dissolve in water to make exactly 1000 mL.

Standard Glyoxal Solution Dilute Standard Glyoxal Stock Solution to 10 times with ethanol (99.5). Prepare before use. Each mL of this solution contains 2 μg of glyoxal ($C_2H_2O_2$).

Standard Glyoxal Stock Solution Transfer a quantity of 40% glyoxal TS, equivalent to 0.200 g of glyoxal, in a 100-mL volumetric flask, and dilute to 100 mL with ethanol (99.5). Dilute to 100-fold with ethanol (99.5) before use. Each mL of this solution contains 20 μg of glyoxal ($C_2H_2O_2$).

9.41 Reagents, Test Solutions

Add the following:

4-Amino-6-chlorobenzene-1,3-disulfonamide
$C_6H_8ClN_3O_4S_2$ White, crystals or crystalline powder.

Identification—Determine the infrared absorption spectrum of 4-amino-6-chlorobenzene-1,3-disulfonamide as directed in the potassium bromide disk method under Infrared Spectrophotometry <2.25>: it exhibits absorption at the wave numbers of about 3380 cm^{-1}, 3250 cm^{-1}, 1638 cm^{-1}, 1597 cm^{-1}, 1544 cm^{-1} and 1324 cm^{-1}.

Storage—Preserve in tight containers.

Bilirubin for assay $C_{33}H_{36}N_4O_6$ A red-orange powder. Very slightly soluble in dimethyl sulfoxide, and practically insoluble in water and in ethanol (99.5).

Identification Determine the infrared absorption spectrum of bilirubin for assay as directed in the ATR method under Infrared Spectrophotometry <2.25>: it exhibits absorption at the wave numbers of about 3400 cm^{-1}, 2910 cm^{-1}, 1686 cm^{-1} and 1643 cm^{-1}.

Absorbance <2.24> $E^{1\%}_{1\,cm}$ (453 nm): 970 – 1134 (1 mg, dimethyl sulfoxide, 200 mL). Conduct this procedure without exposure to light, using light-resistant vessels.

Purity Related substances—Conduct this procedure without exposure to light, using light-resistant vessels. The following sample solution and standard solution should be prepared before use. Dissolve 5 mg of bilirubin for assay in 50 mL of a warmed mixture of dimethyl sulfoxide and acetic acid (100) (9:1), cool and use this solution as the sample solution. Pipet 1 mL of the sample solution, add a mixture of dimethyl sulfoxide and acetic acid (100) (9:1) to

make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine each peak area by the automatic integration method: the total area of the peaks other than bilirubin obtained from the sample solution is not larger than the peak area of bilirubin from the standard solution.
Operating conditions

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay under Oriental Bezoar.

Time span of measurement: About 3 times as long as the retention time of bilirubin, beginning after the solvent peak.
System suitability

System performance and system repeatability: Proceed as directed in the system suitability in the Assay under Oriental Bezoar.

Deuterated acetone for nuclear magnetic resonance spectroscopy CD_3COCD_3 Prepared for nuclear magnetic resonance spectroscopy.

Diclofenac sodium for assay $C_{14}H_{10}Cl_2NNaO_2$ [Same as the monograph Diclofenac Sodium. When dried, it contains not less than 99.0% of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$).]

Diisopropyl 1,3-dithiolan-2-ylidenemalonate
$C_{12}H_{18}O_4S_2$ White crystals.

Identification—Determine the absorption spectrum of a solution of diisopropyl 1,3-dithiolan-2-ylidenemalonate in methanol (1 in 125,000) as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits a maximum between 304 nm and 308 nm.

Melting point <2.60>: 54 – 57°C

Dilute phenolphthalein TS See phenolphthalein TS, dilute.

Euodia fruit [Same as the namesake monograph]

Evodiamine for assay $C_{19}H_{17}N_3O$ White to light yellow, crystals or crystalline powder. Very slightly soluble in methanol and in ethanol (99.5), and practically insoluble in water. Correct the content based on the amount (%) obtained in the Assay.

Identification—Proceed as directed in the Assay: it exhibits a double doublet-like signal equivalent to one proton around δ 2.82 ppm, signals equivalent to four protons which includes a singlet signal around δ 2.91 ppm and a multiplet signal around δ 2.90 ppm – δ 2.98 ppm, a double triplet-like signal equivalent to one proton around δ 3.23 ppm, a double doublet-like signal equivalent to one proton around δ 4.66 ppm, a singlet signal equivalent to one proton around δ 6.16 ppm, a triplet-like signal equivalent to one proton around δ 7.00 ppm, a triplet-like signal equivalent to one proton around δ 7.05 ppm, a doublet-like signal equivalent to one proton around δ 7.08 ppm, a triplet-like signal equivalent to one proton around δ 7.14 ppm, a doublet-like signal equivalent to one proton around δ 7.39 ppm, a doublet-like signal equivalent to one proton around δ 7.51 ppm, a multiplet signal equivalent to one proton around δ 7.52 ppm and a double doublet-like signal equivalent to one proton around δ 7.83 ppm.

Unity of peak—Dissolve 1 mg of evodiamine for assay in 20 mL of methanol, and use this solution as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography <2.01> according to the following conditions, and compare the absorption spectra of at least 3 points including the top of evodiamine peak and around the two middle peak heights of before and after the top: no difference in form is observed among their spectra.
Operating conditions

Column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay (1) under Goshuyuto Extract.

Detector: A photodiode array detector (wavelength: 282 nm: spectrum range of measurement: 220 – 400 nm).
System suitability

System performance: When the procedure is run with 10 μL of the sample solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of evodiamine are not less than 5000 and not more than 1.5, respectively.

Assay—Weigh accurately 5 mg of evodiamine for assay and 1 mg of DSS-d_6 for nuclear magnetic resonance spectroscopy using an ultramicrobalance, dissolve them in 1 mL of deuterated dimethylsulfoxide for nuclear magnetic resonance spectroscopy, and use this solution as the sample solution. Transfer the sample solution into an NMR tube 5 mm in outer diameter, and measure ^{1}H-NMR as directed under Nuclear Magnetic Resonance Spectroscopy <2.21> and Crude Drugs Test <5.01> according to the following conditions, using DSS-d_6 for nuclear magnetic resonance spectroscopy as the internal reference compound. Calculate the resonance intensity A (equivalent to 1 hydrogen) of the signal around δ 6.16 ppm assuming the signal of the internal reference compound as δ 0 ppm.

$$\text{Amount (\%) of evodiamine } (C_{19}H_{17}N_3O) = M_S \times I \times P/(M \times N) \times 1.3521$$

M: Amount (mg) of evodiamine for assay taken
M_S: Amount (mg) of DSS-d_6 for nuclear magnetic resonance spectroscopy taken
I: Signal resonance intensity A based on the signal resonance intensity of DSS-d_6 for nuclear magnetic resonance spectroscopy as 9.000
N: Number of the hydrogen derived from A
P: Purity (%) of DSS-d_6 for nuclear magnetic resonance spectroscopy

Operating conditions

Apparatus: A nuclear magnetic resonance spectrometer having ^{1}H resonance frequency of not less than 400 MHz.

Target nucleus: ^{1}H.

Digital resolution: 0.25 Hz or lower.

Measuring spectrum range: 20 ppm or upper, including

between −5 ppm and 15 ppm.

Spinning: off.

Pulse angle: 90°.

^{13}C decoupling: on.

Delay time: Repeating pulse waiting time not less than 60 seconds.

Integrating times: 8 or more times.

Dummy scanning: 2 or more times.

Measuring temperature: A constant temperature between 20°C and 30°C.

System suitability

Test for required detectability: When the procedure is run with the sample solution under the above operating conditions, the SN ratio of the signal around δ 6.16 ppm is not less than 100.

System performance: When the procedure is run with the sample solution under the above operating conditions, the signals around δ 6.16 ppm is not overlapped with any signal of obvious foreign substance.

System repeatability: When the test is repeated 6 times with the sample solution under the above operating conditions, the relative standard deviation of the ratio of the resonance intensity A to that of the internal reference compound is not more than 1.0%.

Felodipine for assay [Same as the monograph Felodipine. It contains not less than 99.5% of ferodipine ($C_{18}H_{19}Cl_2NO_4$), calculated on the dried basis.]

40% glyoxal TS *Content:* 38 – 42%. Assay—Put 1.000 g of 40% glyoxal TS in a glass-stoppered flask, add 20 mL of a solution of hydroxylammonium chloride (7 in 100) and 50 mL of water. Stopper tightly, allow to stand for 30 minutes, titrate <2.50> with 1 mol/L sodium hydroxide VS (indicator: 1.0 mL of methyl red-methylene blue TS). Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 1 mol/L sodium hydroxide VS
= 29.02 mg of $C_2H_2O_2$

Iodoethane for assay C_2H_5I Colorless to slightly yellow liquid, turning brown on exposure to air and light. Miscible with ethanol (95). Specific gravity d_{20}^{20}: about 1.95; Boiling point: about 72°C.

Refractive index <2.45> n_D^{20}: 1.509 – 1.515.

Content: not less than 99.0%. Assay—Proceed as directed in the Assay under isopropyl iodide for assay.

Each mL of 0.1 mol/L silver nitrate VS
= 15.60 mg of C_2H_5I

Storage—Preserve in tight, light-resistant containers.

Iron (III) chloride-amidosulfuric acid TS Dissolve 10 g of iron (III) chloride hexahydrate and 16 g of amidosulfuric acid (standard reagent) in water to make 1000 mL.

Lanoconazole $C_{14}H_{10}ClN_3S_2$ [Same as the namesake monograph]

(*Z*)-Ligustilide TS for thin-layer chromatography Dissolve 1 mg of (*Z*)-ligustilide for thin-layer chromatography in 10 mL of methanol.

Methyl 4-aminobenzoate $H_2NC_6H_4COOCH_3$ Pale yellow, crystals or crystalline powder.

Melting point <2.60>: 111 – 114°C

3-Methyl-2-benzothiazolonehydrazone hydrochloride monohydrate $C_8H_{10}ClN_3S.H_2O$ A white to light yellow-white crystalline powder. Melting point: about 270°C (with decomposition).

Methyl red-sodium hydroxide TS Dissolve 50 mg of methyl red in a mixture of 1.86 mL of 0.1 mol/L sodium hydroxide VS and 50 mL of ethanol (95), and add water to make 100 mL.

Nortriptyline hydrochloride $C_{19}H_{21}N.HCl$ [Same as the namesake monograph]

Nortriptyline hydrochloride for assay $C_{19}H_{21}N.HCl$ [Same as the monograph Nortriptyline Hydrochloride. When dried, it contains not less than 99.0% of nortriptyline hydrochloride ($C_{19}H_{21}N.HCl$).]

Peucedanum·ledebourielloides for purity Powder of the root and rhizome of *Peucedanum ledebourielloides* K. T. Fu (*Umbelliferae*).

Identification—Place 1.0 g of peucedanum·ledebourielloides for purity in a glass-stoppered centrifuge tube, add 5 mL of hexane, shake for 10 minutes, centrifuge, and use the supernatant liquid as the sample solution. Perform the test with the sample solution as directed under Thin-layer Chromatography <2.03>. Spot 5 μL of the sample solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of hexane, ethyl acetate and acetic acid (100) (20:10:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): blue fluorescent spots at *R*f values of about 0.35 (agasyllin) and about 0.4 [xanthalin ($C_{24}H_{26}O_7$)] are observed.

Phenolphthalein TS, dilute Dissolve 0.1 g of phenolphthalein in 80 mL of ethanol (95), and add water to make 100 mL.

Platycodin D for thin-layer chromatography $C_{57}H_{92}O_{28}$ A white powder. Freely soluble in methanol.

Identification Determine the infrared absorption spectrum of platycodin D for thin-layer chromatography as directed in the potassium bromide disk method under Infrared Spectrophotometry <2.25>: it exhibits absorption at the wave numbers of about 1734 cm^{-1}, 1637 cm^{-1}, 1385 cm^{-1}, 825 cm^{-1} and 783 cm^{-1}.

Purity Related substances—Dissolve 2 mg of platycodin D for thin-layer chromatography in 2 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <2.03>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chro-

matography. Develop the plate with a mixture of 1-propanol, ethyl acetate, water and acetic acid (100) (5:3:2:1) to a distance of about 10 cm, and air-dry the plate. Spray dilute sulfuric acid on the plate, and heat the plate at 105°C for 10 minutes: the spots other than the principal spot with an *R*f value of about 0.5 from the sample solution are not more intense than the spot from the standard solution.

Sodium stearyl fumarate $C_{22}H_{39}NaO_4$ A white crystalline powder.

Identification (1) Determine the infrared absorption spectrum of sodium stearyl fumarate as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>: it exhibits absorption at the wave numbers of about 2950 cm^{-1}, 2920 cm^{-1}, 2850 cm^{-1}, 1720 cm^{-1}, 1610 cm^{-1}, 1313 cm^{-1}, 1186 cm^{-1}, 980 cm^{-1}, and 665 cm^{-1}.

(2) Sodium stearyl fumarate responds to Qualitative Tests <*1.09*> (1) for sodium salt.

Valsartan $C_{24}H_{29}N_5O_3$ [Same as the namesake monograph]

Change the following as follows:

Cineol for assay $C_{10}H_{18}O$ Clear and colorless liquid, having a characteristic aroma.

Refractive index <*2.45*> n_D^{20}: 1.457 – 1.459

Specific gravity <*2.56*> d_{20}^{20}: 0.920 – 0.930

Purity Related substances—Dissolve 0.10 g of cineol for assay in 25 mL of hexane and use this solution as the sample solution. Perform the test with 2 μL of the sample solution as directed under Gas Chromatography <*2.02*> according to the following conditions. Determine each peak area by the automatic integration method and calculate the amount of them by the area percentage method: the total amount of the peaks other than cineol is not more than 1.0%.

Operating conditions

Proceed the operating conditions in the Assay under Eucalyptus Oil except test for required detectability and time span of measurement.

Test for required detectability: To 1 mL of the sample solution add hexane to make 100 mL. Adjust so that the peak height of cineol obtained with 2 μL of this solution is 40 to 60% of the full scale.

Time span of measurement: About 3 times as long as the retention time of cineol, beginning after the solvent peak.

(*E*)-Ferulic acid for assay $C_{10}H_{10}O_4$ (*E*)-Ferulic acid. It meets the requirements of the following 1) (*E*)-ferulic acid for assay 1 or 2) (*E*)-ferulic acid for assay 2 (Purity value by quantitative NMR). The former is used after drying in a desiccator (silica gel) for 24 hours, and latter is used with correction for its amount based on the result obtained in the Assay.

1) (*E*)-Ferulic acid for assay 1

Absorbance <*2.24*> $E_{1\,cm}^{1\%}$ (320 nm): 878 – 969 (5 mg, methanol, 1000 mL).

Purity Related substances—Conduct this procedure without exposure to light, using light-resistant vessels. Dissolve 5 mg of (*E*)-ferulic acid for assay 1 in 10 mL of a mixture of water and methanol (1:1), and use this solution as the sample solution. Pipet 1 mL of the sample solution, add a mixture of water and methanol (1:1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine each peak area by the automatic integration method: the total area of the peaks other than (*E*)-ferulic acid obtained from the sample solution is not larger than the peak area of (*E*)-ferulic acid from the standard solution.

Operating conditions

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay (1) under Tokishakuyakusan Extract.

Time span of measurement: About 6 times as long as the retention time of (*E*)-ferulic acid, beginning after the solvent peak.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add a mixture of water and methanol (1:1) to make exactly 20 mL. Confirm that the peak area of (*E*)-ferulic acid obtained with 10 μL of this solution is equivalent to 3.5 to 6.5% of that with 10 μL of the standard solution.

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of (*E*)-ferulic acid are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of (*E*)-ferulic acid is not more than 1.5%.

2) (*E*)-Ferulic acid for assay 2 (Purity value by quantitative NMR)

Unity of peak—Conduct this procedure without exposure to light, using light-resistant vessels. Dissolve 5 mg of (*E*)-ferulic acid for assay 2 in 10 mL of a mixture of water and methanol (1:1), and use this solution as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and compare the absorption spectra of at least 3 points including the top of (*E*)-ferulic acid peak and around the two middle peak heights of before and after the top: no difference in form is observed among their spectra.

Operating conditions

Column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay (1) under Tokishakuyakusan Extract.

Detector: A photodiode array detector (wavelength: 320 nm, measuring range of spectrum: 220 – 400 nm).

System suitability

System performance: When the procedure is run with 10 μL of the sample solution under the above operating conditions, the number of theoretical plates and the symmetry

factor of the peak of (*E*)-ferulic acid are not less than 5000 and not more than 1.5, respectively.

Assay—Weigh accurately 5 mg of (*E*)-ferulic acid for assay 2 and 1 mg of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy using an ultramicrobalance, dissolve in 1 mL of deuterated methanol for nuclear magnetic resonance spectroscopy, and use this solution as the sample solution. Transfer the sample solution into an NMR tube 5 mm in outer diameter, and measure ^{1}H-NMR as directed under Nuclear Magnetic Resonance Spectroscopy <*2.21*> and Crude Drugs Test <*5.01*> according to the following conditions, using 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy as the internal reference compound. Calculate the resonance intensity A (equivalent to 1 hydrogen) of the signal around δ 6.06 ppm assuming the signal of the internal reference compound as δ 0 ppm.

$$\text{Amount (\%) of (}E\text{)-ferulic acid } (C_{10}H_{10}O_4) = M_S \times I \times P/(M \times N) \times 0.8573$$

M: Amount (mg) of (*E*)-ferulic acid for assay 2 taken
M_S: Amount (mg) of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy taken
I: Signal resonance intensity A based on the signal resonance intensity of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy as 18.000
N: Number of hydrogen derived from A
P: Purity (%) of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy

Operating conditions

Apparatus: A nuclear magnetic resonance spectrometer having ^{1}H resonance frequency of not less than 400 MHz.

Target nucleus: ^{1}H.

Digital resolution: 0.25 Hz or lower.

Measuring spectrum range: 20 ppm or upper, including between −5 ppm and 15 ppm.

Spinning: off.

Pulse angle: 90°.

^{13}C decoupling: on.

Delay time: Repeating pulse waiting time not less than 60 seconds.

Integrating times: 8 or more times.

Dummy scanning: 2 or more times.

Measuring temperature: A constant temperature between 20°C and 30°C.

System suitability

Test for required detectability: When the procedure is run with the sample solution under the above operating conditions, the SN ratio of the signal around δ 6.06 ppm is not less than 100.

System performance: When the procedure is run with the sample solution under the above operating conditions, the signal around δ 6.06 ppm is not overlapped with any signal of obvious foreign substances.

System repeatability: When the test is repeated 6 times with the sample solution under the above operating conditions, the relative standard deviation of the ratio of the resonance intensity A to that of the internal reference compound is not more than 1.0%.

10-Hydroxy-2-(*E*)-decenoic acid for assay $C_{10}H_{18}O_3$ 10-hydroxy-2-(*E*)-decenoic acid for thin-layer chromatography. It meets the requirement of the following 1) 10-Hydroxy-2-(*E*)-decenoic acid for assay 1 or 2) 10-Hydroxy-2-(*E*)-decenoic acid for assay 2 (Purity value by quantitative NMR). The latter is used with correction for its amount based on the result obtained in the Assay.

1) 10-Hydroxy-2-(*E*)-decenoic acid for assay 1

Purity Related substances—Dissolve 10 mg of 10-hydroxy-2-(*E*)-decenoic acid for assay 1 in 100 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the total area of the peaks other than 10-hydroxy-2-(*E*)-decenoic acid obtained from the sample solution is not larger than the peak area of 10-hydroxy-2-(*E*)-decenoic acid from the standard solution.

Operating conditions

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay under Royal Jelly.

Time span of measurement: About 4 times as long as the retention time of 10-hydroxy-2-(*E*)-decenoic acid, beginning after the solvent peak.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add methanol to make exactly 20 mL. Confirm that the peak area of 10-hydroxy-2-(*E*)-decenoic acid obtained with 10 μL of this solution is equivalent to 3.5 to 6.5% of that with 10 μL of the standard solution.

System performance: Dissolve 1 mg of propyl parahydroxybenzoate for resolution check in 10 mL of the sample solution. When the procedure is run with 10 μL of this solution under the above operating conditions, 10-hydroxy-2-(*E*)-decenoic acid and propyl parahydroxybenzoate are eluted in this order with the resolution between these peaks being not less than 6.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of 10-hydroxy-2-(*E*)-decenoic acid is not more than 1.5%.

2) 10-Hydroxy-2-(*E*)-decenoic acid for assay 2 (Purity value by quantitative NMR)

Unity of peak—Dissolve 1 mg of 10-hydroxy-2-(*E*)-decenoic acid for assay 2 in 50 mL of methanol, and use this solution as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and compare the absorption spectra of at least 3 points including the top of 10-hydroxy-2-(*E*)-decenoic acid peak and around the two middle peak heights of before and after the

top: no difference in form is observed among their spectra.
Operating conditions

Column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay under Royal Jelly.

Detector: A photodiode array detector (wavelength: 215 nm: spectrum range of measurement: 200 – 400 nm).
System suitability

System performance: Dissolve 1 mg each of 10-hydroxy-2-(*E*)-decenoic acid for assay 2 and propyl parahydroxybenzoate for resolution check in methanol to make 50 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, 10-hydroxy-2-(*E*)-decenoic acid and propyl parahydroxybenzoate are eluted in this order with the resolution between these peaks being not less than 6.

Assay—Weigh accurately 5 mg of 10-hydroxy-2-(*E*)-decenoic acid for assay 2 and 1 mg of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy using an ultramicrobalance, dissolve in 1 mL of deuterated methanol for nuclear magnetic resonance spectroscopy, and use this solution as the sample solution. Transfer the sample solution into an NMR tube 5 mm in outer diameter, and measure ^{1}H-NMR as directed under Nuclear Magnetic Resonance Spectroscopy ⟨*2.21*⟩ and Crude Drugs Test ⟨*5.01*⟩ according to the following conditions, using 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy as the internal reference compound. Calculate the resonance intensities, A_1 (equivalent to 1 hydrogen) and A_2 (equivalent to 1 hydrogen), of the signals around δ 5.54 ppm and δ 6.70 ppm assuming the signal of the internal reference compound as δ0 ppm.

Amount (%) of 10-hydroxy-2-(*E*)-decenoic acid ($C_{10}H_{18}O_3$)
$= M_S \times I \times P/(M \times N) \times 0.8223$

M: Amount (mg) of 10-hydroxy-2-(*E*)-decenoic acid for assay 2 taken
M_S: Amount (mg) of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy taken
I: Sum of the signal resonance intensities, A_1 and A_2, based on the signal resonance intensity of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy as 18.000
N: Sum of the numbers of the hydrogen derived from A_1 and A_2
P: Purity (%) of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy

Operating conditions

Apparatus: A nuclear magnetic resonance spectrometer having ^{1}H resonance frequency of not less than 400 MHz.

Target nucleus: ^{1}H.

Digital resolution: 0.25 Hz or lower.

Measuring spectrum range: 20 ppm or upper, including between −5 ppm and 15 ppm.

Spinning: off.

Pulse angle: 90°.

^{13}C decoupling: on.

Delay time: Repeating pulse waiting time not less than 60 seconds.

Integrating times: 8 or more times.

Dummy scanning: 2 or more times.

Measuring temperature: A constant temperature between 20°C and 30°C.
System suitability

Test for required detectability: When the procedure is run with the sample solution under the above operating conditions, the SN ratio of each signal around δ 5.54 ppm and δ 6.70 ppm is not less than 100.

System performance: When the procedure is run with the sample solution under the above operating conditions, the signals around δ 5.54 ppm and δ 6.70 ppm are not overlapped with any signal of obvious foreign substances, and the ratio of the resonance intensities, A_1/A_2, of each signal around δ 5.54 ppm and δ 6.70 ppm is between 0.99 and 1.01.

System repeatability: When the test is repeated 6 times with the sample solution under the above operating conditions, the relative standard deviations of the ratios of the resonance intensities, A_1 and A_2, to that of the internal reference are not more than 1.0%.

Limonene $C_{10}H_{16}$ Clear and colorless liquid, having a characteristic aroma and a bitter taste.

Refractive index ⟨*2.45*⟩ n_D^{20}: 1.472 – 1.474

Specific gravity ⟨*2.56*⟩ d_{20}^{20}: 0.841 – 0.846

Purity Related substances—Dissolve 0.1 g of limonene in 25 mL of hexane and use this solution as the sample solution. Perform the test with 2 μL of the sample solution as directed under Gas Chromatography ⟨*2.02*⟩ according to the following conditions. Determine each peak area by the automatic integration method and calculate the amount of them by the area percentage method: the total amount of the peaks other than limonene is not more than 3.0%.
Operating conditions

Proceed the operating conditions in the Assay under Eucalyptus Oil except test for required detectability and time span of measurement.

Test for required detectability: To 1 mL of the sample solution add hexane to make 100 mL. Adjust so that the peak height of limonene obtained with 2 μL of this solution is 40 to 60% of the full scale.

Time span of measurement: About 3 times as long as the retention time of limonene, beginning after the solvent peak.

Saikosaponin a for thin-layer chromatography A white, crystalline powder or powder. Freely soluble in methanol and in ethanol (99.5), and practically insoluble in water. Melting point: 225 – 232°C (with decomposition).

Absorbance ⟨*2.24*⟩ $E_{1\,cm}^{1\%}$ (206 nm): 65 – 73 (15 mg, methanol, 200 mL). Previously dried in a desiccator (in vacuum, silica gel) for 24 hours.

Purity Related substances—Dissolve 1.0 mg of saikosaponin a for thin-layer chromatography in exactly 1 mL of methanol, and perform the test with 10 μL of this solution as directed in the Identification (2) under Bupleurum

Root: any spot other than the principal spot at the *R*f value of about 0.4 does not appear.

Saikosaponin d for assay $C_{42}H_{68}O_{13}$ A white, crystalline powder or powder. Freely soluble in methanol and in ethanol (99.5), and practically insoluble in water. Melting point: about 240°C.

Absorbance ⟨*2.24*⟩ $E^{1\%}_{1\,cm}$ (206 nm): 66 – 74 (15 mg, methanol, 200 mL). Previously dried in a desiccator (in vacuum, silica gel) for 24 hours.

Purity Related substances—

(1) Dissolve 2.0 mg of saikosaponin d for assay in 2 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Proceed the test with 10 μL each of the sample solution and standard solution as directed in the Identification (2) under Bupleurum Root: the spot other than the principal spot around *R*f value of 0.4 obtained from the sample solution is not larger and not more intense than the spot from the standard solution.

(2) Dissolve 10 mg of saikosaponin d for assay in 20 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine each peak area by the automatic integration method: the total area of the peaks other than saikosaponin d obtained from the sample solution is not larger than the peak area of saikosaponin d from the standard solution.

Operating conditions

Detector and column: Proceed as directed in the operating conditions in the Assay under Bupleurum Root.

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of water and acetonitrile (11:9).

Flow rate: Adjust so that the retention time of saikosaponin d is about 13 minutes.

Time span of measurement: About 4 times as long as the retention time of saikosaponin d, beginning after the solvent peak.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add methanol to make exactly 20 mL. Confirm that the peak area of saikosaponin d obtained with 20 μL of this solution is equivalent to 3.5 to 6.5% of that with 20 μL of the standard solution.

System performance: Dissolve 6 mg each of saikosaponin d for assay and saikosaponin a for assay in methanol to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, saikosaponin a and saikosaponin d are eluted in this order with the resolution between these peaks being not less than 1.5.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of saikosaponin d is not more than 1.0%.

Sinomenine for assay $C_{19}H_{23}NO_4$ Sinomenine for thin-layer chromatography. It meets the requirements of the following 1) sinomenine for assay 1 or 2) sinomenine for assay 2 (Purity value by quantitative NMR). The former is used after drying in a desiccator (silica gel) for 24 hours, and latter is used with correction for its amount based on the result obtained in the Assay.

1) Sinomenine for assay 1

Identification Determine the absorption spectrum of a solution of sinomenine for assay in methanol (1 in 25,000) as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩: it exhibits the maximum between 259 nm and 263 nm.

Purity Related substances—Dissolve 5 mg of sinomenine for assay 1 in 10 mL of a mixture of water and acetonitrile (7:3), and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mixture of water and acetonitrile (7:3) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine each peak area by the automatic integration method: the total area of the peaks other than sinomenine obtained from the sample solution is not larger than the peak area of sinomenine from the standard solution.

Operating conditions

Column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay (1) under Boiogito Extract.

Detector: An ultraviolet absorption photometer (wavelength: 261 nm).

Time span of measurement: About 3 times as long as the retention time of sinomenine, beginning after the solvent peak.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add a mixture of water and acetonitrile (7:3) to make exactly 20 mL. Confirm that the peak area of sinomenine obtained with 10 μL of this solution is equivalent to 3.5 to 6.5% of that with 10 μL of the standard solution.

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of sinomenine are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sinomenine is not more than 1.5%.

2) Sinomenine for assay 2 (Purity value by quantitative NMR)

Unity of peak—Dissolve 5 mg of sinomenine for assay 2 in 10 mL of a mixture of water and acetonitrile (7:3), and

use this solution as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography <2.01> according to the following conditions, and compare the absorption spectra of at least 3 points including the top of sinomenine peak and around the two middle peak heights of before and after the top: no difference in form is observed among their spectra.

Operating conditions

Column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay (1) under Boiogito Extract.

Detector: A photodiode array detector (wavelength: 261 nm, spectrum range of requirement: 220 – 400 nm).

System suitability

System performance: When the procedure is run with 10 μL of the sample solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of sinomenine are not less than 5000 and not more than 1.5, respectively.

Assay—Weigh accurately 5 mg of sinomenine for assay 2 and 1 mg of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy using an ultramicrobalance, dissolve in 1 mL of deuterated acetone for nuclear magnetic resonance spectroscopy, and use this solution as the sample solution. Transfer the sample solution into an NMR tube 5 mm in outer diameter, and measure ^{1}H-NMR as directed under Nuclear Magnetic Resonance Spectroscopy <2.21> and Crude Drugs Test <5.01> according to the following conditions, using 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy as the internal reference compound. Calculate the resonance intensity A (equivalent to 1 hydrogen) of the signal around δ 5.42 ppm assuming the signal of the internal reference compound as δ 0 ppm.

$$\text{Amount (\%) of sinomenine } (C_{19}H_{23}NO_4) = M_S \times I \times P/(M \times N) \times 1.4543$$

M: Amount (mg) of sinomenine for assay 2 taken
M_S: Amount (mg) of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy taken
I: Signal resonance intensity A based on the signal resonance intensity of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy as 18.000
N: Number of hydrogen derived from A
P: Purity (%) of 1,4-BTMSB-d_4 for nuclear magnetic resonance spectroscopy

Operating conditions

Apparatus: A nuclear magnetic resonance spectrometer having ^{1}H resonance frequency of not less than 400 MHz.

Target nucleus: ^{1}H.

Digital resolution: 0.25 Hz or lower.

Measuring spectrum range: 20 ppm or upper, including between −5 ppm and 15 ppm.

Spinning: off.

Pulse angle: 90°.

^{13}C decoupling: on.

Delay time: Repeating pulse waiting time not less than 60 seconds.

Integrating times: 8 or more times.

Dummy scanning: 2 or more times.

Measuring temperature: A constant temperature between 20°C and 30°C.

System suitability

Test for required detectability: When the procedure is run with the sample solution under the above operating conditions, the SN ratio of the signal around δ 5.42 ppm is not less than 100.

System performance: When the procedure is run with the sample solution under the above operating conditions, the signal around δ 5.42 ppm is not overlapped with any signal of obvious foreign substances.

System repeatability: When the test is repeated 6 times with the sample solution under the above operating conditions, the relative standard deviation of the ratio of the resonance intensity A to that of the internal reference compound is not more than 1.0%.

Starch, soluble [K 8659, Starch, soluble, First class]

9.42 Solid Supports/Column Packings for Chromatography

Add the following:

Amylose tris-(3,5-dimethylphenylcarbamate)-coated silica gel for liquid chromatography Prepared for liquid chromatography.

Octadecyl-strong anion exchange-silanized silica gel for liquid chromatography Prepared for liquid chromatography.

Porous silica gel for gas chromatography Prepared for gas chromatography.

Official Monographs

Amphotericin B Tablets

アムホテリシン B 錠

Add the following next to the Uniformity of dosage units:

Disintegration ⟨*6.09*⟩ Perform the test using the disk: it meets the requirement.

Beclometasone Dipropionate

ベクロメタゾンプロピオン酸エステル

Change the Description and Optical rotation as follows:

Description Beclometasone Dipropionate occurs as a white to pale yellow powder.

It is soluble in methanol, sparingly soluble in ethanol (99.5), and practically insoluble in water.

Melting point: about 208°C (with decomposition).

It shows crystal polymorphism.

Optical rotation ⟨*2.49*⟩ $[\alpha]_D^{25}$: +106 – +114° (after drying, 0.1 g, ethanol (99.5), 10 mL, 100 mm).

Betamethasone Dipropionate

ベタメタゾンジプロピオン酸エステル

Change the Description and Optical rotation as follows:

Description Betamethasone Dipropionate occurs as a white to pale yellow-white crystalline powder. It is odorless.

It is freely soluble in acetone and in chloroform, soluble in methanol and in ethanol (99.5), and practically insoluble in water.

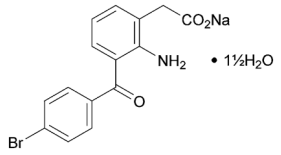
It is gradually affected by light.

Optical rotation ⟨*2.49*⟩ $[\alpha]_D^{25}$: +84 – +89° (after drying, 50 mg, ethanol (99.5), 10 mL, 100 mm).

Add the following:

Bromfenac Sodium Hydrate

ブロムフェナクナトリウム水和物



$C_{15}H_{11}BrNNaO_3.1½H_2O$: 383.17

Sodium 2-[2-amino-3-(4-bromobenzoyl)phenyl]acetate sesquihydrate

[*120638-55-3*]

Bromfenac Sodium Hydrate contains not less than 97.5% and not more than 101.5% of bromfenac sodium ($C_{15}H_{11}BrNNaO_3$: 356.15), calculated on the anhydrous basis.

Description Bromfenac Sodium Hydrate occurs as a yellow to orange crystalline powder.

It is freely soluble in water, soluble in methanol, and slightly soluble in ethanol (99.5).

It dissolves in a solution of sodium hydrogen carbonate (21 in 2500).

Identification **(1)** Dissolve 10 mg of Bromfenac Sodium Hydrate in 500 mL of a solution of sodium hydrogen carbonate (21 in 2500). Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Bromfenac Sodium RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Bromfenac Sodium Hydrate as directed in the potassium bromide disk method under Infrared Spectrophotometry ⟨*2.25*⟩, and compare the spectrum with the Reference Spectrum or the spectrum of Bromfenac Sodium RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) A solution of Bromfenac Sodium Hydrate (1 in 20) responds to Qualitative Tests ⟨*1.09*⟩ (1) for sodium salt.

pH ⟨*2.54*⟩ Dissolve 1.0 g of Bromfenac Sodium Hydrate in 20 mL of water: the pH of the solution is between 8.4 and 10.2.

Purity **(1)** Heavy metals ⟨*1.07*⟩—Proceed with 1.0 g of Bromfenac Sodium Hydrate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL

of Standard Lead Solution (not more than 20 ppm).

(2) Related substances—Dissolve 50 mg of Bromfenac Sodium Hydrate in 100 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine each peak area by the automatic integration method: the area of the peak other than bromfenac obtained from the sample solution is not larger than 1/10 times the peak area of bromfenac from the standard solution, and the total area of the peaks other than bromfenac from the sample solution is not larger than the peak area of bromfenac from the standard solution.

Operating conditions—

Detector, column and column temperature: Proceed as directed in the operating conditions in the Assay.

Mobile phase: Dissolve 3.85 g of ammonium acetate in 1000 mL of water, and adjust to pH 4.0 with acetic acid (100). To 570 mL of this solution add 430 mL of acetonitrile.

Flow rate: Adjust so that the retention time of bromfenac is about 8 minutes.

Time span of measurement: About 3 times as long as the retention time of bromfenac, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 2 mL of the standard solution, and add methanol to make exactly 20 mL. Confirm that the peak area of bromfenac obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of bromfenac are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of bromfenac is not more than 2.0%.

Water <*2.48*> 6.9 – 8.5% (0.15 g, volumetric titration, direct titration. Use a solution of imidazole for water determination in methanol for water determination (1 in 80) instead of methanol for water determination).

Assay Weigh accurately about 30 mg each of Bromfenac Sodium Hydrate and Bromfenac Sodium RS (separately determine the water <*2.48*> in the same manner as Bromfenac Sodium Hydrate), dissolve each in methanol to make exactly 50 mL. Pipet 5 mL each of these solutions, add the mobile phase to make them exactly 100 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of bromfenac in each solution.

Amount (mg) of bromfenac sodium ($C_{15}H_{11}BrNNaO_3$) = $M_S \times A_T/A_S$

M_S: Amount (mg) of Bromfenac Sodium RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 266 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35°C.

Mobile phase: Dissolve 3.85 g of ammonium acetate in 1000 mL of water. To 600 mL of this solution add 250 mL of methanol and 150 mL of tetrahydrofuran.

Flow rate: Adjust so that the retention time of bromfenac is about 9 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of bromfenac are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of bromfenac is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Add the following:

Bromfenac Sodium Ophthalmic Solution

ブロムフェナクナトリウム点眼液

Bromfenac Sodium Ophthalmic Solution is an aqueous ophthalmic preparation.

It contains not less than 90.0% and not more than 110.0% of the labeled amount of Bromfenac Sodium Hydrate ($C_{15}H_{11}BrNNaO_3.1½H_2O$: 383.17).

Method of preparation Prepare as directed under Ophthalmic Liquids and Solutions, with Bromfenac Sodium Hydrate.

Description Bromfenac Sodium Ophthalmic Solution occurs as a clear and yellow liquid.

Identification To a volume of Bromfenac Sodium Ophthalmic Solution, equivalent to 1 mg of Bromfenac Sodium Hydrate, add a solution of sodium hydrogen carbonate (21

in 2500) to make 50 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits maxima between 266 nm and 270 nm, and between 377 nm and 381 nm.

pH Being specified separately when the drug is granted approval based on the Law.

Purity Related substances—Being specified separately when the drug is granted approval based on the Law.

Foreign insoluble matter <*6.11*> It meets the requirement.

Insoluble particulate matter <*6.08*> It meets the requirement.

Sterility <*4.06*> Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Pipet a volume of Bromfenac Sodium Ophthalmic Solution, equivalent to about 2 mg of bromfenac sodium hydrate ($C_{15}H_{11}BrNNaO_3.1½H_2O$), add the mobile phase to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of Bromfenac Sodium RS (separately determine the water <*2.48*> in the same manner as Bromfenac Sodium Hydrate), and dissolve in the mobile phase to make exactly 20 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of bromfenac in each solution.

Amount (mg) of bromfenac sodium hydrate ($C_{15}H_{11}BrNNaO_3.1½H_2O$)
$= M_S \times A_T/A_S \times 1/10 \times 1.076$

M_S: Amount (mg) of Bromfenac Sodium RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 266 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: Dissolve 1.98 g of diammonium hydrogen phosphate in 750 mL of water, adjust to pH 7.3 with phosphoric acid, and add 250 mL of acetonitrile.

Flow rate: Adjust so that the retention time of bromfenac is about 18 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of bromfenac are not less than 13,000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of bromfenac is not more than 1.0%.

Containers and storage Containers—Tight containers.

Change the following as follows:

Anhydrous Dibasic Calcium Phosphate

無水リン酸水素カルシウム

$CaHPO_4$: 136.06
[*7757-93-9*]

This monograph is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Anhydrous Dibasic Calcium Phosphate contains not less than 97.5% and not more than 102.5% of dibasic calcium phosphate ($CaHPO_4$).

◆**Description** Anhydrous Dibasic Calcium Phosphate occurs as white, crystalline powder or granules.

It is practically insoluble in water and in ethanol (99.5).

It dissolves in dilute hydrochloric acid and in dilute nitric acid.◆

Identification **(1)** Dissolve 0.1 g of Anhydrous Dibasic Calcium Phosphate in 10 mL of 2 mol/L hydrochloric acid TS by warming, add 2.5 mL of ammonia TS dropwise with shaking, and add 5 mL of ammonium oxalate TS: a white precipitate is produced.

(2) Dissolve 0.1 g of Anhydrous Dibasic Calcium Phosphate in 5 mL of dilute nitric acid, and add 2 mL of hexaammonium heptamolybdate TS after warming at 70°C for 1 to 2 minutes: a yellow precipitate is produced.

Purity **(1)** Acid-insoluble substances—Dissolve 5.0 g of Anhydrous Dibasic Calcium Phosphate in 40 mL of water and 10 mL of hydrochloric acid, and boil gently for 5 minutes. After cooling, collect the insoluble substance using a filter paper for assay. Wash with water until no more turbidity of the washings is produced when silver nitrate TS is added. Ignite to incinerate the residue and the filter paper at 600 ± 50°C: the mass is not more than 10 mg (not more than 0.2%).

(2) Chloride—To 0.20 g of Anhydrous Dibasic Calcium Phosphate add 20 mL of water and 13 mL of dilute nitric acid, dissolve by warming, if necessary, add water to make

100 mL, and filter, if necessary. Put 50 mL of this solution in a Nessler tube, and use this as the sample solution. Separately, transfer 0.70 mL of 0.01 mol/L hydrochloric acid VS to another Nessler tube, add 6 mL of dilute nitric acid and water to make 50 mL, and use this solution as the control solution. Add 1 mL of silver nitrate TS to the sample solution and control solution, mix well, and allow to stand for 5 minutes protecting from light. Compare the opalescence developed in both solutions against a black background by viewing down-ward or transversely. The opalescence developed in the sample solution is not more than that of the control solution (not more than 0.25%).

(3) Sulfate—Dissolve 0.50 g of Anhydrous Dibasic Calcium Phosphate in 5 mL of water and 5 mL of dilute hydrochloric acid, add water to make 100 mL, and filter, if necessary. Put 20 mL of this solution in a Nessler tube, add 1 mL of dilute hydrochloric acid, and add water to make 50 mL, and use this as the sample solution. Transfer 1.0 mL of 0.005 mol/L sulfuric acid VS to another Nessler tube, add 1 mL of dilute hydrochloride acid and water to make 50 mL, and use this solution as the control solution. Add 2 mL of barium chloride TS to the sample solution and control solution, mix well, and allow to stand for 10 minutes. Compare the white turbidity produced in both solutions against a black background by viewing downward or transversely. The turbidity produced in the sample solution is not thicker than that of the control solution (not more than 0.48%).

(4) Carbonate—Mix 1.0 g of Anhydrous Dibasic Calcium Phosphate with 5 mL of freshly boiled and cooled water, and add immediately 2 mL of hydrochloric acid: no effervescence occurs.

◇**(5)** Heavy metals ⟨*1.07*⟩—Dissolve 0.65 g of Anhydrous Dibasic Calcium Phosphate in a mixture of 5 mL of water and 5 mL of dilute hydrochloric acid by warming, cool, and add ammonia TS until precipitates begin to form in the solution. Dissolve the precipitates by adding a small amount of dilute hydrochloric acid dropwise, add 10 mL of hydrochloric acid-ammonium acetate buffer solution (pH 3.5) and water to make 50 mL, and perform the test using this solution as the sample solution. Prepare the control solution as follows: to 10 mL of hydrochloric acid-ammonium acetate buffer solution (pH 3.5) add 2.0 mL of Standard Lead Solution and water to make 50 mL (not more than 31 ppm).◇

(6) Barium—Heat 0.5 g of Anhydrous Dibasic Calcium Phosphate with 10 mL of water, add 1 mL of hydrochloric acid dropwise with stirring, and filter after cooling, if necessary. Add 2 mL of potassium sulfate TS to this solution, and allow to stand for 10 minutes: no turbidity forms.

◆**(7)** Arsenic ⟨*1.11*⟩—Dissolve 1.0 g of Anhydrous Dibasic Calcium Phosphate in 5 mL of dilute hydrochloric acid, and perform the test with this solution as the test solution (not more than 2 ppm).◆

Loss on ignition ⟨*2.43*⟩ Not less than 6.6% and not more than 8.7% (1 g, 800 – 825°C, constant mass).

Assay Weigh accurately about 0.4 g of Anhydrous Dibasic Calcium Phosphate, dissolve in 12 mL of dilute hydrochloric acid by heating on a water bath, if necessary, and add water to make exactly 200 mL. Pipet 20 mL of this solution, add exactly 25 mL of 0.02 mol/L disodium dihydrogen ethylenediamine tetraacetate VS, 50 mL of water and 5 mL of ammonia-ammonium chloride buffer solution (pH 10.7), and titrate ⟨*2.50*⟩ the excess disodium dihydrogen ethylenediamine tetraacetate with 0.02 mol/L zinc sulfate VS (indicator: 25 mg of eriochrome black T-sodium chloride indicator). Perform a blank determination in the same manner.

Each mL of 0.02 mol/L disodium dihydrogen ethylenediamine tetraacetate VS
= 2.721 mg of $CaHPO_4$

◆**Containers and storage** Containers—Well-closed containers.◆

Add the following:

Cefalotin Sodium for Injection

注射用セファロチンナトリウム

Cefalotin Sodium for Injection is a preparation for injection, which is dissolved before use.

It contains not less than 90.0% and not more than 110.0% of the labeled potency of cefalotin ($C_{16}H_{16}N_2O_6S_2$: 396.44).

Method of preparation Prepare as directed under Injections, with Cefalotin Sodium.

Description Cefalotin Sodium for Injection occurs as white to light yellow-white, crystals or crystalline powder.

Identification Determine the infrared absorption spectrum of Cefalotin Sodium for Injection as directed in the potassium bromide disk method under Infrared Spectrophotometry ⟨*2.25*⟩, and compare the spectrum with the Reference Spectrum of Cefalotin Sodium or the spectrum of Cefalotin Sodium RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

pH ⟨*2.54*⟩ Dissolve an amount of Cefalotin Sodium for Injection, equivalent to 0.5 g (potency) of Cefalotin Sodium, in 5 mL of water: the pH of the solution is between 4.5 and 7.0.

Purity **(1)** Clarity and color of solution—Dissolve 1.0 g of Cefalotin Sodium for Injection in 10 mL of water: the solution is clear. Perform the test with this solution as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩: the absorbance at 450 nm is not more than 0.20.

(2) Related substances—Dissolve an amount of Cefalotin Sodium for Injection, equivalent to 25 mg (potency), in the mobile phase to make 25 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solu-

tion as directed under Liquid Chromatography <2.01> according to the following conditions, and determine each peak area by the automatic integration method: the area of the peak other than cefalotin obtained from the sample solution is not larger than the peak area of cefalotin from the standard solution, and the total area of the peaks other than cefalotin from the sample solution is not larger than 3 times the peak area of cefalotin from the standard solution.

Operating conditions—

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay under Cefalotin Sodium.

Time span of measurement: About 4 times as long as the retention time of cefalotin.

System suitability—

Proceed as directed in the system suitability in the Purity (4) under Cefalotin Sodium.

Water <2.48> Not more than 1.0% (0.5 g, volumetric titration, back titration).

Bacterial endotoxins <4.01> Less than 0.2 EU/mg (potency).

Uniformity of dosage units <6.02> It meets the requirement of the Mass variation test.

Foreign insoluble matter <6.06> Perform the test according to Method 2: it meets the requirement.

Insoluble particulate matter <6.07> It meets the requirement.

Sterility <4.06> Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Weigh accurately the mass of the contents of not less than 10 containers of Cefalotin Sodium for Injection. Weigh accurately an amount of the contents, equivalent to about 25 mg (potency) of Cefalotin Sodium, dissolve in the mobile phase to make exactly 25 mL, and use this solution as the sample solution. Separately, weigh accurately about 25 mg (potency) of Cefalotin Sodium RS, and dissolve in the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay under Cefalotin Sodium.

Amount [μg(potency)] of cefalotin ($C_{16}H_{16}N_2O_6S_2$) $= M_S \times A_T/A_S \times 1000$

M_S: Amount [mg(potency)] of Cefalotin Sodium RS taken

Containers and storage Containers—Hermetic containers.

Add the following:

Cefixime Fine Granules

セフィキシム細粒

Cefixime Fine Granules contain not less than 90.0% and not more than 105.0% of the labeled potency of cefixime ($C_{16}H_{15}N_5O_7S_2$: 453.45).

Method of preparation Prepare as directed under Granules, with Cefixime Hydrate.

Identification To a quantity of powdered Cefixime Fine Granules, equivalent to 2 mg (potency) of Cefixime Hydrate add 150 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), and shake. If necessary, filter or centrifuge. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits maximum between 286 nm and 290 nm.

Purity Related substances—To a quantity of powdered Cefixime Fine Granules, equivalent to 0.1 g (potency) of Cefixime Hydrate, add 100 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake, filter through a membrane filter with a pore size not exceeding 0.45 μm, and use the filtrate as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic integration method, and calculate their amounts by the area percentage method: the amount of the peak other than cefixime is not more than 1.0%, and the total amount of the peaks other than cefixime is not more than 2.5%.

Operating conditions—

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay under Cefixime Hydrate.

Time span of measurement: Proceed as directed in the operating conditions in the Purity under Cefixime Hydrate.

System suitability—

Test for required detectability: To 1 mL of the sample solution add 0.1 mol/L phosphate buffer solution (pH 7.0) to make 100 mL, and use this solution as the solution for system suitability test. Pipet 1 mL of the solution for system suitability test, and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 10 mL. Confirm that the peak area of cefixime obtained with 10 μL of this solution is equivalent to 7 to 13% of that with 10 μL of the solution for system suitability test.

System performance: When the procedure is run with 10 μL of the solution for system suitability test under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of cefixime are not less than 4000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of cefixime is not more than 2.0%.

Water ⟨*2.48*⟩ Not more than 3.0% (1 g, volumetric titration, direct titration. Use a mixture of formamide for water determination and methanol for water determination (2:1) instead of methanol for water determination).

Uniformity of dosage units ⟨*6.02*⟩ Perform the test according to the following method: Cefixime Fine Granules in single-dose packages meet the requirement of the Content uniformity test.

To the total content of 1 package of Cefixime Fine Granules add 7 V/10 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly V mL so that each mL contains about 1 mg (potency) of Cefixime Hydrate. Centrifuge this solution, pipet 10 mL of the supernatant liquid, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately an amount of Cefixime RS, equivalent to about 20 mg (potency), dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay under Cefixime Hydrate.

Amount [mg (potency)] of cefixime ($C_{16}H_{15}N_5O_7S_2$)
$= M_S \times A_T/A_S \times V/20$

M_S: Amount [mg (potency)] of Cefixime RS taken

Dissolution ⟨*6.10*⟩ When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rates in 30 minutes of Cefixime Fine Granules is not less than 75%.

Start the test with an accurately weighed amount of Cefixime Fine Granules, equivalent to about 0.1 g (potency) of Cefixime Hydrate, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 10 mL of the first filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately an amount of Cefixime RS, equivalent to about 28 mg (potency), and dissolve in the dissolution medium to make exactly 50 mL. Pipet 4 mL of this solution, add the dissolution medium to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine the peak areas, A_T and A_S, of cefixime in each solution.

Dissolution rate (%) with respect to the labeled amount of cefixime ($C_{16}H_{15}N_5O_7S_2$)
$= M_S/M_T \times A_T/A_S \times 1/C \times 360$

M_S: Amount [mg (potency)] of Cefixime RS taken
M_T: Amount (g) of Cefixime Fine Granules taken
C: Labeled amount [mg (potency)] of cefixime ($C_{16}H_{15}N_5O_7S_2$) in 1 g

Operating conditions—

Proceed as directed in the operating conditions in the Assay under Cefixime Hydrate.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of cefixime are not less than 4000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of cefixime is not more than 2.0%.

Assay Weigh accurately an amount of powdered Cefixime Fine Granules, equivalent to about 0.1 g (potency) of Cefixime Hydrate, add 70 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake, and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL. Centrifuge this solution, pipet 10 mL of the supernatant liquid, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately an amount of Cefixime RS, equivalent to about 20 mg (potency), dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay under Cefixime Hydrate.

Amount [mg (potency)] of cefixime ($C_{16}H_{15}N_5O_7S_2$)
$= M_S \times A_T/A_S \times 5$

M_S: Amount [mg (potency)] of Cefixime RS taken

Containers and storage Containers—Tight containers.

Change the following as follows:

Microcrystalline Cellulose

結晶セルロース

[*9004-34-6*, cellulose]

This monograph is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Microcrystalline Cellulose is purified, partially depolymerized α-cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

The label indicates the ◇mean degree of polymerization, loss on drying,◇ and bulk density values with a range.

◆**Description** Microcrystalline Cellulose occurs as a white crystalline powder having fluidity.

It is practically insoluble in water, in ethanol (95) and in diethyl ether.

It swells with sodium hydroxide TS on heating.◆

Identification **(1)** Dissolve 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water, add 0.5 g of iodine, and shake for 15 minutes. Place about 10 mg of Microcrystalline Cellulose on a watch glass, and disperse in 2 mL of this solution: the substance develops a blue-violet color.

(2) Determine the infrared absorption spectrum of Microcrystalline Cellulose as directed in the ATR method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the spectrum of Microcrystalline Cellulose RS for Identification: both spectra exhibit similar intensities of absorption at the same wave numbers. If there are absorptions between 800 cm^{-1} and 825 cm^{-1}, and between 950 cm^{-1} and 1000 cm^{-1}, disregard the absorptions.

(3) Transfer about 1.3 g of Microcrystalline Cellulose, accurately weighed, to a 125-mL conical flask, and add exactly 25 mL each of water and 1 mol/L cupriethylenediamine TS. Immediately purge the solution with nitrogen, insert the stopper, and shake on a suitable mechanical shaker to dissolve. Perform the test with a suitable amount of this solution, taken exactly, according to Method 1 under Viscosity Determination <*2.53*> using a capillary viscometer having the viscosity constant (K) of approximately 0.03, at 25 ± 0.1°C, and determine the kinematic viscosity, v. Separately, perform the test with a mixture of exactly 25 mL each of water and 1 mol/L cupriethylenediamine TS in the same manner as above, using a capillary viscometer having K of approximately 0.01, and determine the kinematic viscosity, v_0.

Calculate the relative viscosity, η_{rel}, of Microcrystalline Cellulose by the following formula:

$$\eta_{rel} = v/v_0$$

Obtain the product, $[\eta]C$, of intrinsic viscosity $[\eta]$(mL/g) and concentration C (g/100 mL) from the value η_{rel} of the table. When calculate the degree of polymerization, P, by the following formula, P is not more than 350 ◇and within the labeled range.◇

$$P = 95[\eta]C/M_T$$

M_T: Amount (g) of the Microcrystalline Cellulose taken, calculated on the dried basis

pH <*2.54*> Shake 5.0 g of Microcrystalline Cellulose with 40 mL of water for 20 minutes, and centrifuge: the pH of the supernatant liquid is between 5.0 and 7.5.

Purity ◇**(1)** Heavy metals <*1.07*>—Proceed with 2.0 g of Microcrystalline Cellulose according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).◇

(2) Water-soluble substances—Shake 5.0 g of Microcrystalline Cellulose with 80 mL of water for 10 minutes, filter with the aid of vacuum through a filter paper for quantitative analysis (5C) into a vacuum flask. Evaporate the filtrate in a tared evaporating dish to dryness without charring, dry at 105°C for 1 hour, cool in a desiccator, and weigh: the difference between the mass of the residue and the mass obtained from a blank determination does not exceed 12.5 mg.

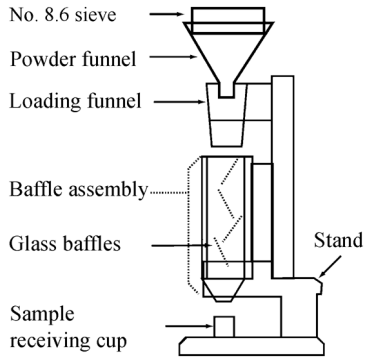
(3) Diethyl ether-soluble substances—Place 10.0 g of Microcrystalline Cellulose in a column having an internal diameter of about 20 mm, and pass 50 mL of peroxide-free diethyl ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporation dish. Dry the residue at 105°C for 30 minutes, allow to cool in a desiccator, and weigh: the difference between the mass of the residue and the mass obtained from a blank determination does not exceed 5.0 mg.

Conductivity <*2.51*> Perform the test as directed in the Conductivity Measurement with the supernatant liquid obtained in the pH as the sample solution, and determine the conductivity at 25 ± 0.1°C. Determine in the same manner the conductivity of water used for the preparation of the sample solution: the difference between these conductivities is not more than 75 $\mu S \cdot cm^{-1}$.

Loss on drying <*2.41*> Not more than 7.0% ◇and within a range as specified on the label◇ (1 g, 105°C. 3 hours).

Residue on ignition <*2.44*> Not more than 0.1% (2 g).

Bulk density (i) Apparatus—Use a volumeter shown in the figure. Put a No.8.6 sieve (2000 μm) on the top of the volumeter. A funnel is mounted over a baffle box, having four glass baffle plates inside which the sample powder slides as it passes. At the bottom of the baffle box is a funnel that collect the powder, and allows it to pour into a sample receiving cup mounted directly below it.



(ii) Procedure—Weigh accurately the mass of a brass or stainless steel cup, which has a capacity of 25.0 ± 0.05 mL and an inside diameter of 30.0 ± 2.0 mm, and put the cup directly below the funnel of the volumeter. Slowly pour Microcrystalline Cellulose 5.1 cm height from the upper part of the powder funnel through the sieve, at a rate suitable to prevent clogging, until the cup overflows. If the clogging occurs, take out the sieve. Level the excess powder with the aid of a slide glass, weigh the filled cup, and weigh accurately the content of the cup, and then calculate the bulk

Table for Conversion of Relative Viscosity (η_{rel}) into the Product of Limiting Viscosity and Concentration ($[\eta]C$)

	$[\eta]C$									
η_{rel}	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
1.1	0.098	0.106	0.115	0.125	0.134	0.143	0.152	0.161	0.170	0.180
1.2	0.189	0.198	0.207	0.216	0.225	0.233	0.242	0.250	0.259	0.268
1.3	0.276	0.285	0.293	0.302	0.310	0.318	0.326	0.334	0.342	0.350
1.4	0.358	0.367	0.375	0.383	0.391	0.399	0.407	0.414	0.422	0.430
1.5	0.437	0.445	0.453	0.460	0.468	0.476	0.484	0.491	0.499	0.507
1.6	0.515	0.522	0.529	0.536	0.544	0.551	0.558	0.566	0.573	0.580
1.7	0.587	0.595	0.602	0.608	0.615	0.622	0.629	0.636	0.642	0.649
1.8	0.656	0.663	0.670	0.677	0.683	0.690	0.697	0.704	0.710	0.717
1.9	0.723	0.730	0.736	0.743	0.749	0.756	0.762	0.769	0.775	0.782
2.0	0.788	0.795	0.802	0.809	0.815	0.821	0.827	0.833	0.840	0.846
2.1	0.852	0.858	0.864	0.870	0.876	0.882	0.888	0.894	0.900	0.906
2.2	0.912	0.918	0.924	0.929	0.935	0.941	0.948	0.953	0.959	0.965
2.3	0.971	0.976	0.983	0.988	0.994	1.000	1.006	1.011	1.017	1.022
2.4	1.028	1.033	1.039	1.044	1.050	1.056	1.061	1.067	1.072	1.078
2.5	1.083	1.089	1.094	1.100	1.105	1.111	1.116	1.121	1.126	1.131
2.6	1.137	1.142	1.147	1.153	1.158	1.163	1.169	1.174	1.179	1.184
2.7	1.190	1.195	1.200	1.205	1.210	1.215	1.220	1.225	1.230	1.235
2.8	1.240	1.245	1.250	1.255	1.260	1.265	1.270	1.275	1.280	1.285
2.9	1.290	1.295	1.300	1.305	1.310	1.314	1.319	1.324	1.329	1.333
3.0	1.338	1.343	1.348	1.352	1.357	1.362	1.367	1.371	1.376	1.381
3.1	1.386	1.390	1.395	1.400	1.405	1.409	1.414	1.418	1.423	1.427
3.2	1.432	1.436	1.441	1.446	1.450	1.455	1.459	1.464	1.468	1.473
3.3	1.477	1.482	1.486	1.491	1.496	1.500	1.504	1.508	1.513	1.517
3.4	1.521	1.525	1.529	1.533	1.537	1.542	1.546	1.550	1.554	1.558
3.5	1.562	1.566	1.570	1.575	1.579	1.583	1.587	1.591	1.595	1.600
3.6	1.604	1.608	1.612	1.617	1.621	1.625	1.629	1.633	1.637	1.642
3.7	1.646	1.650	1.654	1.658	1.662	1.666	1.671	1.675	1.679	1.683
3.8	1.687	1.691	1.695	1.700	1.704	1.708	1.712	1.715	1.719	1.723
3.9	1.727	1.731	1.735	1.739	1.742	1.746	1.750	1.754	1.758	1.762
4.0	1.765	1.769	1.773	1.777	1.781	1.785	1.789	1.792	1.796	1.800
4.1	1.804	1.808	1.811	1.815	1.819	1.822	1.826	1.830	1.833	1.837
4.2	1.841	1.845	1.848	1.852	1.856	1.859	1.863	1.867	1.870	1.874
4.3	1.878	1.882	1.885	1.889	1.893	1.896	1.900	1.904	1.907	1.911
4.4	1.914	1.918	1.921	1.925	1.929	1.932	1.936	1.939	1.943	1.946
4.5	1.950	1.954	1.957	1.961	1.964	1.968	1.971	1.975	1.979	1.982
4.6	1.986	1.989	1.993	1.996	2.000	2.003	2.007	2.010	2.013	2.017
4.7	2.020	2.023	2.027	2.030	2.033	2.037	2.040	2.043	2.047	2.050
4.8	2.053	2.057	2.060	2.063	2.067	2.070	2.073	2.077	2.080	2.083
4.9	2.087	2.090	2.093	2.097	2.100	2.103	2.107	2.110	2.113	2.116
5.0	2.119	2.122	2.125	2.129	2.132	2.135	2.139	2.142	2.145	2.148
5.1	2.151	2.154	2.158	2.160	2.164	2.167	2.170	2.173	2.176	2.180
5.2	2.183	2.186	2.190	2.192	2.195	2.197	2.200	2.203	2.206	2.209
5.3	2.212	2.215	2.218	2.221	2.224	2.227	2.230	2.233	2.236	2.240
5.4	2.243	2.246	2.249	2.252	2.255	2.258	2.261	2.264	2.267	2.270
5.5	2.273	2.276	2.279	2.282	2.285	2.288	2.291	2.294	2.297	2.300
5.6	2.303	2.306	2.309	2.312	2.315	2.318	2.320	2.324	2.326	2.329
5.7	2.332	2.335	2.338	2.341	2.344	2.347	2.350	2.353	2.355	2.358
5.8	2.361	2.364	2.367	2.370	2.373	2.376	2.379	2.382	2.384	2.387
5.9	2.390	2.393	2.396	2.400	2.403	2.405	2.408	2.411	2.414	2.417
6.0	2.419	2.422	2.425	2.428	2.431	2.433	2.436	2.439	2.442	2.444
6.1	2.447	2.450	2.453	2.456	2.458	2.461	2.464	2.467	2.470	2.472
6.2	2.475	2.478	2.481	2.483	2.486	2.489	2.492	2.494	2.497	2.500
6.3	2.503	2.505	2.508	2.511	2.513	2.516	2.518	2.521	2.524	2.526
6.4	2.529	2.532	2.534	2.537	2.540	2.542	2.545	2.547	2.550	2.553
6.5	2.555	2.558	2.561	2.563	2.566	2.568	2.571	2.574	2.576	2.579
6.6	2.581	2.584	2.587	2.590	2.592	2.595	2.597	2.600	2.603	2.605
6.7	2.608	2.610	2.613	2.615	2.618	2.620	2.623	2.625	2.627	2.630
6.8	2.633	2.635	2.637	2.640	2.643	2.645	2.648	2.650	2.653	2.655
6.9	2.658	2.660	2.663	2.665	2.668	2.670	2.673	2.675	2.678	2.680

	$[\eta]C$									
η_{rel}	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
7.0	2.683	2.685	2.687	2.690	2.693	2.695	2.698	2.700	2.702	2.705
7.1	2.707	2.710	2.712	2.714	2.717	2.719	2.721	2.724	2.726	2.729
7.2	2.731	2.733	2.736	2.738	2.740	2.743	2.745	2.748	2.750	2.752
7.3	2.755	2.757	2.760	2.762	2.764	2.767	2.769	2.771	2.774	2.776
7.4	2.779	2.781	2.783	2.786	2.788	2.790	2.793	2.795	2.798	2.800
7.5	2.802	2.805	2.807	2.809	2.812	2.814	2.816	2.819	2.821	2.823
7.6	2.826	2.828	2.830	2.833	2.835	2.837	2.840	2.842	2.844	2.847
7.7	2.849	2.851	2.854	2.856	2.858	2.860	2.863	2.865	2.868	2.870
7.8	2.873	2.875	2.877	2.879	2.881	2.884	2.887	2.889	2.891	2.893
7.9	2.895	2.898	2.900	2.902	2.905	2.907	2.909	2.911	2.913	2.915
8.0	2.918	2.920	2.922	2.924	2.926	2.928	2.931	2.933	2.935	2.937
8.1	2.939	2.942	2.944	2.946	2.948	2.950	2.952	2.955	2.957	2.959
8.2	2.961	2.963	2.966	2.968	2.970	2.972	2.974	2.976	2.979	2.981
8.3	2.983	2.985	2.987	2.990	2.992	2.994	2.996	2.998	3.000	3.002
8.4	3.004	3.006	3.008	3.010	3.012	3.015	3.017	3.019	3.021	3.023
8.5	3.025	3.027	3.029	3.031	3.033	3.035	3.037	3.040	3.042	3.044
8.6	3.046	3.048	3.050	3.052	3.054	3.056	3.058	3.060	3.062	3.064
8.7	3.067	3.069	3.071	3.073	3.075	3.077	3.079	3.081	3.083	3.085
8.8	3.087	3.089	3.092	3.094	3.096	3.098	3.100	3.102	3.104	3.106
8.9	3.108	3.110	3.112	3.114	3.116	3.118	3.120	3.122	3.124	3.126
9.0	3.128	3.130	3.132	3.134	3.136	3.138	3.140	3.142	3.144	3.146
9.1	3.148	3.150	3.152	3.154	3.156	3.158	3.160	3.162	3.164	3.166
9.2	3.168	3.170	3.172	3.174	3.176	3.178	3.180	3.182	3.184	3.186
9.3	3.188	3.190	3.192	3.194	3.196	3.198	3.200	3.202	3.204	3.206
9.4	3.208	3.210	3.212	3.214	3.215	3.217	3.219	3.221	3.223	3.225
9.5	3.227	3.229	3.231	3.233	3.235	3.237	3.239	3.241	3.242	3.244
9.6	3.246	3.248	3.250	3.252	3.254	3.256	3.258	3.260	3.262	3.264
9.7	3.266	3.268	3.269	3.271	3.273	3.275	3.277	3.279	3.281	3.283
9.8	3.285	3.287	3.289	3.291	3.293	3.295	3.297	3.298	3.300	3.302
9.9	3.304	3.305	3.307	3.309	3.311	3.313	3.316	3.318	3.320	3.321
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
10	3.32	3.34	3.36	3.37	3.39	3.41	3.43	3.45	3.46	3.48
11	3.50	3.52	3.53	3.55	3.56	3.58	3.60	3.61	3.63	3.64
12	3.66	3.68	3.69	3.71	3.72	3.74	3.76	3.77	3.79	3.80
13	3.80	3.83	3.85	3.86	3.88	3.89	3.90	3.92	3.93	3.95
14	3.96	3.97	3.99	4.00	4.02	4.03	4.04	4.06	4.07	4.09
15	4.10	4.11	4.13	4.14	4.15	4.17	4.18	4.19	4.20	4.22
16	4.23	4.24	4.25	4.27	4.28	4.29	4.30	4.31	4.33	4.34
17	4.35	4.36	4.37	4.38	4.39	4.41	4.42	4.43	4.44	4.45
18	4.46	4.47	4.48	4.49	4.50	4.52	4.53	4.54	4.55	4.56
19	4.57	4.58	4.59	4.60	4.61	4.62	4.63	4.64	4.65	4.66

density by the following expression: the bulk density is within the labeled specification.

$$\text{Bulk density (g/cm}^3\text{)} = A/25$$

A: Measured mass (g) of the content of the cup

Microbial limit *<4.05>* The acceptance criteria of TAMC and TYMC are 10^3 CFU/g and 10^2 CFU/g, respectively. *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are not observed.

◆**Containers and storage** Containers—Tight containers.◆

Chloramphenicol

クロラムフェニコール

Delete the Purity (2), move up (3) to (2) and change (2) as follows:

Purity

(2) Related substances—Dissolve 0.10 g of Chloramphenicol in 10 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 10 mL of the standard solution (1), add methanol to make exactly 20 mL, and use this

solution as the standard solution (2). Perform the test with these solutions as directed under Thin-layer Chromatography ⟨*2.03*⟩. Spot 20 μL each of the sample solution and standard solutions (1) and (2) on a plate of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of ethyl acetate, methanol and acetic acid (100) (10:1:1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot and the spot of the starting point obtained from the sample solution are not more intense than the spot from the standard solution (1), and the total amount of these spots from the sample solution is not more than 2.0%.

Change the Assay as follows:

Assay Weigh accurately an amount of Chloramphenicol and Chloramphenicol RS, equivalent to about 50 mg (potency), dissolve each in 10 mL of methanol, and add water to make exactly 50 mL. Pipet 20 mL each of these solutions, and add water to make exactly 100 mL. Pipet 10 mL each of these solutions, add water to make exactly 100 mL, and use these solutions as the sample solution and standard solution. Determine the absorbances, A_T and A_S, of the sample solution and standard solution at 278 nm as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩.

Amount [μg (potency)] of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$) $= M_S \times A_T/A_S \times 1000$

M_S: Amount [mg (potency)] of Chloramphenicol RS taken

Chlorpromazine Hydrochloride

クロルプロマジン塩酸塩

Change the Melting point as follows:

Melting point ⟨*2.60*⟩ 196 – 200°C

Cholesterol

コレステロール

Change the Description and Optical rotation as follows:

Description Cholesterol occurs as white to pale yellow, crystals or grains. It is odorless, or has a slight odor. It is tasteless.

It is freely soluble in chloroform and in diethyl ether, sparingly soluble in ethanol (99.5) and in acetone, and practically insoluble in water.

It gradually changes to a yellow to light yellow-brown color by light.

Optical rotation ⟨*2.49*⟩ $[\alpha]_D^{25}$: −29 – −36° (after drying, 0.2 g, acetone, 10 mL, 100 mm).

Add the following:

Clarithromycin for Syrup

シロップ用クラリスロマイシン

Clarithromycin for Syrup is a preparation for syrup, which is suspended before use.

It contains not less than 90.0% and not more than 110.0% of the labeled potency of clarithromycin ($C_{38}H_{69}NO_{13}$: 747.95).

Method of preparation Prepare as directed under Preparations for Syrups, with Clarithromycin.

Identification To an amount of Clarithromycin for Syrup, equivalent to 0.1 g (potency) of Clarithromycin, add 5 mL of acetone, and sonicate. After cooling with ice, centrifuge, take the supernatant liquid, and evaporate the solvent. Dissolve 10 mg of the residue and 2 mg of Clarithromycin RS in separate 2 mL of acetone, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with these solutions as directed under Thin-layer Chromatography ⟨*2.03*⟩. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, ethyl acetate and acetic acid (100) (90:10:1) to a distance of about 15 cm, and air-dry the plate. Spray evenly sulfuric acid on the plate, and heat the plate at 105°C for 10 minutes: the principal spot obtained from the sample solution and the spot from the standard solution show a black-purple color and the same *R*f value.

Water ⟨*2.48*⟩ Not more than 3.0% (0.5 g, volumetric titration, direct titration).

Uniformity of dosage units ⟨*6.02*⟩ Perform the test according to the following method: Clarithromycin for Syrup in single-dose packages meet the requirement of the Content uniformity test.

To the total content of 1 package of Clarithromycin for Syrup add $3V/5$ mL of ethanol (99.5), add exactly $V/10$ mL of the internal standard solution, sonicate with occasional vigorous shaking, and add ethanol (99.5) to make V mL so that each mL contains about 0.5 mg (potency) of Clarithromycin. Centrifuge this solution, and filter the supernatant liquid through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 3 mL of the filtrate, and use the subsequent filtrate as the sample solution. Then, proceed as directed in the Assay.

Amount [mg (potency)] of clarithromycin ($C_{38}H_{69}NO_{13}$) $= M_S \times Q_T/Q_S \times V/100$

M_S: Amount [mg (potency)] of Clarithromycin RS taken

Internal standard solution—A solution of butyl parahydroxybenzoate in ethanol (99.5) (1 in 12,500).

Dissolution ⟨*6.10*⟩ When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of disodium hydrogen phosphate-citric acid buffer

solution (pH 5.5) as the dissolution medium, the dissolution rate in 90 minutes of Clarithromycin for Syrup is not less than 75%.

Start the test with an accurately weighed amount of Clarithromycin for Syrup, equivalent to about 50 mg (potency) of Clarithromycin, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 10 mL of the first filtrate, pipet 10 mL of the subsequent filtrate, add the mobile phase to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately an amount of Clarithromycin RS, equivalent to about 28 mg (potency), and dissolve in acetonitrile for liquid chromatography to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 100 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of clarithromycin in each solution.

Dissolution rate (%) with respect to the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$)
$= M_S/M_T \times A_T/A_S \times 1/C \times 180$

M_S: Amount [mg (potency)] of Clarithromycin RS taken
M_T: Amount (g) of Clarithromycin for Syrup taken
C: Labeled amount of [mg (potency)] of clarithromycin ($C_{38}H_{69}NO_{13}$) in 1 g

Operating conditions—
Proceed as directed in the operating conditions in the Assay.
System suitability—
System performance: When the procedure is run with 100 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of clarithromycin are not less than 3000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 100 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of clarithromycin is not more than 2.0%.

Assay Weigh accurately an amount of crushed Clarithromycin for Syrup, equivalent to about 50 mg (potency) of Clarithromycin, add 60 mL of ethanol (99.5), add exactly 10 mL of the internal standard solution, sonicate with occasional vigorous shaking, and add ethanol (99.5) to make 100 mL. Centrifuge this solution, and filter the supernatant liquid through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 3 mL of the filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately an amount of Clarithromycin RS, equivalent about 50 mg (potency), and dissolve in ethanol (99.5) to make exactly 50 mL. Pipet 10 mL of this solution, add exactly 2 mL of the internal standard solution, add ethanol (99.5) to make 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of clarithromycin to that of the internal standard.

Amount [mg (potency)] of clarithromycin ($C_{38}H_{69}NO_{13}$)
$= M_S \times Q_T/Q_S$

M_S: Amount [mg (potency)] of Clarithromycin RS taken

Internal standard solution—A solution of butyl parahydroxybenzoate in ethanol (99.5) (1 in 12,500).
Operating conditions—
Detector: An ultraviolet absorption photometer (wavelength: 210 nm).
Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).
Column temperature: A constant temperature of about 50°C.
Mobile phase: A mixture of diluted 0.2 mol/L potassium dihydrogen phosphate TS (1 in 3) and acetonitrile for liquid chromatography (13:7).
Flow rate: Adjust so that the retention time of clarithromycin is about 8 minutes.
System suitability—
System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, clarithromycin and the internal standard are eluted in this order with the resolution between these peaks being not less than 3.
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of clarithromycin to that of the internal standard is not more than 2.0%.

Containers and storage Containers—Tight containers.
Storage—Light-resistant.

Cloperastine Hydrochloride

クロペラスチン塩酸塩

Change the Melting point and Purity (2) as follows:

Melting point <*2.60*> 149 – 153°C

Purity
(2) Related substances—Dissolve 40 mg of Cloperastine Hydrochloride in 50 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine each peak area by the automatic integration method: the area of

the peaks, having the relative retention times of about 0.8 and about 3.0 to cloperastine obtained from the sample solution are not larger than the peak area of cloperastine from the standard solution, and the area of the peak having the relative retention time about 2.0 from the sample solution is not larger than 5/3 times the peak area of cloperastine from the standard solution. The area of the peak other than cloperastine and the peaks mentioned above from the sample solution are not larger than 3/5 times the peak area of cloperastine from the standard solution, and the total area of these peaks is not larger than 2 times the peak area of cloperastine from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 222 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of methanol, 0.1 mol/L potassium dihydrogen phosphate TS and perchloric acid (500:250:1).

Flow rate: Adjust so that the retention time of cloperastine is about 7 minutes.

Time span of measurement: About 4 times as long as the retention time of cloperastine, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 2 mL of the standard solution, add the mobile phase to make exactly 20 mL. Confirm that the peak area of cloperastine obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the standard solution.

System performance: Dissolve 30 mg of Cloperastine Hydrochloride and 40 mg of benzophenone in 100 mL of the mobile phase. To 2 mL of this solution add the mobile phase to make 50 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, cloperastine and benzophenone are eluted in this order with the resolution between these peaks being not less than 6.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of cloperastine is not more than 2.0%.

Dehydrocholic Acid

デヒドロコール酸

Change the Description and Optical rotation as follows:

Description Dehydrocholic Acid occurs as a white crystalline powder. It is odorless, and has a bitter taste.

It is sparingly soluble in acetone, slightly soluble in ethanol (95), and practically insoluble in water.

It dissolves in sodium hydroxide TS.

Optical rotation <*2.49*> $[\alpha]_D^{25}$: +20 – +26° (after drying, 0.2 g, acetone, 10 mL, 100 mm).

Purified Dehydrocholic Acid

精製デヒドロコール酸

Change the Description and Optical rotation as follows:

Description Purified Dehydrocholic Acid occurs as a white crystalline powder. It is odorless, and has a bitter taste.

It is sparingly soluble in acetone, slightly soluble in ethanol (95), and practically insoluble in water.

It dissolves in sodium hydroxide TS.

Optical rotation <*2.49*> $[\alpha]_D^{25}$: +20 – +26° (after drying, 0.2 g, acetone, 10 mL, 100 mm).

Add the following:

Diclofenac Sodium Suppositories

ジクロフェナクナトリウム坐剤

Diclofenac Sodium Suppositories contain not less than 93.0% and not more than 107.0% of the labeled amount of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$: 318.13).

Method of preparation Prepare as directed under Suppositories for Rectal Application, with Diclofenac Sodium.

Identification To an amount of Diclofenac Sodium Suppositories, equivalent to 25 mg of Diclofenac Sodium, add 200 mL of a mixture of methanol and 0.01 mol/L sodium hydroxide TS (99:1), and dissolve by warming. Cool while shaking, add a mixture of methanol and 0.01 mol/L sodium hydroxide TS (99:1) to make 250 mL, and filter through a pledget of absorbent cotton if necessary. To 10 mL of this solution add a mixture of methanol and 0.01 mol/L sodium hydroxide TS (99:1) to make 100 mL. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 280 nm and 284 nm.

Uniformity of dosage unit <*6.02*> Perform the test according to the following method: it meets the requirement of the Content uniformity test.

To 1 suppository of Diclofenac Sodium Suppositories add 5 mL of tetrahydrofuran, and sonicate to dissolve. Add a mixture of methanol and water (3:2) to make exactly 100 mL, shake, and filter through a membrane filter with a pore size not exceeding 0.5 μm. Discard the first 5 mL of the filtrate, pipet V mL of the subsequent filtrate, add a mixture of methanol and water (3:2) to make exactly V' mL so that

each mL contains about 0.125 mg of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$), and use this solution as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$) $= M_S \times A_T/A_S \times V'/V \times 1/4$

M_S: Amount (mg) of diclofenac sodium for assay taken

Melting behavior of suppositories Perform the test according to Method 2 under Melting Point Determination ⟨*2.60*⟩: the melting range is between 33°C and 36°C.

Assay Weigh accurately the mass of not less than 20 Diclofenac Sodium Suppositories, cut into small pieces carefully, and mix uniformly. Weigh accurately a portion of the pieces, equivalent to about 25 mg of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$), add 5 mL of tetrahydrofuran, and sonicate to dissolve. Add a mixture of methanol and water (3:2) to make exactly 100 mL, shake, and filter through a membrane filter with a pore size not exceeding 0.5 μm. Discard the first 5 mL of the filtrate, pipet 10 mL of the subsequent filtrate, add a mixture of methanol and water (3:2) to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 50 mg of diclofenac sodium for assay, previously dried, and dissolve in a mixture of methanol and water (3:2) to make exactly 100 mL. Pipet 5 mL of this solution, add a mixture of methanol and water (3:2) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine the peak areas, A_T and A_S, of diclofenac in each solution.

Amount (mg) of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$) $= M_S \times A_T/A_S \times 1/2$

M_S: Amount (mg) of diclofenac sodium for assay taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.0 mm in inside diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: Dissolve 13.6 g of sodium acetate trihydrate in water to make 1000 mL. To 200 mL of this solution add 300 mL of methanol.

Flow rate: Adjust so that the retention time of diclofenac is about 3.5 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of diclofenac are not less than 2000 and 0.7 to 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of diclofenac is not more than 1.0%.

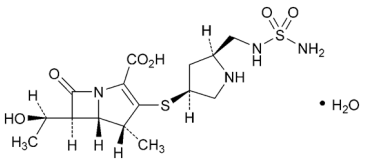
Containers and storage Containers—Tight containers.

Storage—In a cold place.

Add the following:

Doripenem Hydrate

ドリペネム水和物



$C_{15}H_{24}N_4O_6S_2.H_2O$: 438.52

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-{(3*S*,5*S*-5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate [*364622-82-2*]

Doripenem Hydrate contains not less than 970 μg (potency) and not more than 1020 μg (potency) per mg, calculated on the anhydrous basis. The potency of Doripenem Hydrate is expressed as mass (potency) of doripenem ($C_{15}H_{24}N_4O_6S_2$: 420.50).

Description Doripenem Hydrate occurs as a white to pale yellow-brown-white crystalline powder.

It is sparingly soluble in water, slightly soluble in methanol, and practically insoluble in ethanol (99.5).

It is gradually colored to pale yellow-brown-white by light.

Identification (1) Determine the absorption spectrum of a solution of Doripenem Hydrate (1 in 50,000) as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Doripenem RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Doripenem Hydrate as directed in the potassium bromide disk method under Infrared Spectrophotometry ⟨*2.25*⟩, and compare the spectrum with the Reference Spectrum or the spectrum of Doripenem RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Optical rotation ⟨*2.49*⟩ $[\alpha]_D^{20}$: +33 – +38° (0.25 g calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH ⟨*2.54*⟩ Dissolve 0.3 g of Doripenem Hydrate in 30 mL of water: the pH of the solution is between 4.5 and 6.0.

Purity (1) Clarity and color of solution—Dissolve 0.2 g of Doripenem Hydrate in 20 mL of water, and perform the test with this solution as directed under Turbidity Meas-

urement <2.61>: the solution is clear. Perform the test with this solution according to Method 2 under Methods for Color Matching <2.65>: the solution is not more colored than Matching Fluid Y4.

(2) Heavy metals <1.07>—Moisten 1.0 g of Doripenem Hydrate with sulfuric acid, cover loosely, and heat gently to carbonize. Then proceed according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Related substances (i)—Dissolve 20 mg of Doripenem Hydrate in 10 mL of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic integration method: the peak areas of related substance A, having the relative retention time of about 2.2 to doripenem, related substance B, having the relative retention time of about 2.5, and related substance C, having the relative retention time of about 3.2, obtained from the sample solution, are not larger than 1/10 times the peak area of doripenem from the standard solution, and the area of the peak other than doripenem, the peaks mentioned above and the peak having the relative retention time of about 2.1, from the sample solution, is not larger than 1/20 times the peak area of doripenem from the standard solution. Furthermore, the total area of the peaks other than doripenem and the peak having the relative retention time of about 2.1 from the sample solution is not larger than 1/2 times the peak area of doripenem from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30°C.

Mobile phase A: Dissolve 2.04 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust to pH 5.6 – 5.7 with a solution prepared by dissolving 2.61 g of dipotassium hydrogen phosphate in water to make 1000 mL. To 970 mL of this solution add 30 mL of acetonitrile for liquid chromatography.

Mobile phase B: Dissolve 2.04 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust to pH 5.6 – 5.7 with a solution prepared by dissolving 2.61 g of dipotassium hydrogen phosphate in water to make 1000 mL. To 700 mL of this solution add 300 mL of acetonitrile for liquid chromatography.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 15	100	0
15 – 45	100 → 50	0 → 50
45 – 50	50 → 0	50 → 100
50 – 55	0	100

Flow rate: 1.0 mL per minute.

Time span of measurement: For 55 minutes after injection, beginning after the peak having the relative retention time of about 0.2 to doripenem.

System suitability—

Test for required detectability: Pipet 1.5 mL of the standard solution, and add water to make exactly 50 mL. Confirm that the peak area of doripenem obtained with 20 μL of this solution is equivalent to 2.1 to 3.9% of that with 20 μL of the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of doripenem are not less than 5000 and not more than 1.3, respectively.

System repeatability: When the test is repeated 3 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of doripenem is not more than 0.95%.

(ii) Dissolve 20 mg of Doripenem Hydrate in 10 mL of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic integration method: the peak area of related substance D, having the relative retention time of about 0.5 to doripenem, obtained from the sample solution is not larger than 2/5 times the peak area of doripenem from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecyl-strong anion exchange-silanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: To 9 mL of phosphoric acid add 200 mL of water, add 20 mL of triethylamine, and add water to make 2000 mL. Adjust to pH 5.7 – 5.9 with phosphoric acid. To 950 mL of this solution add 50 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of doripenem is about 10 minutes.

System suitability—

Test for required detectability: Pipet 2 mL of the stand-

ard solution, and add water to make exactly 20 mL. Confirm that the peak area of doripenem obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the standard solution.

System performance: To 1 mL of the sample solution add 1 mL of 0.1 mol/L hydrochloric acid TS, allow to stand at 25 ± 5°C for 15 minutes, and add water to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, related substance D and doripenem are eluted in this order with the resolution between these peaks being not less than 5. The number of theoretical plates and the symmetry factor of the peak of related substance D are not less than 300 and 0.7 to 1.3, respectively, and those of the peak of doripenem are not less than 5000 and 0.7 to 1.3, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of doripenem is not more than 2.0%.

(iii) Dissolve 20 mg of Doripenem Hydrate in 10 mL of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the areas of the peaks, having the relative retention time of about 1.8, about 2.2 and about 2.3 to doripenem, obtained from the sample solution are not larger than 1/20, 7/100 and 1/20 times the peak area of doripenem from the standard solution, respectively.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 310 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 30°C.

Mobile phase A: To 11 mL of perchloric acid add water to make 500 mL. To 100 mL of this solution add water to make 1000 mL. To 600 mL of this solution add 100 mL of water, and adjust to pH 1.9 – 2.0 with a solution prepared by adding water to 2.81 g of sodium perchlorate monohydrate to make 1000 mL. To 900 mL of this solution add 100 mL of acetonitrile.

Mobile phase B: To 11 mL of perchloric acid add water to make 500 mL. To 100 mL of this solution add water to make 1000 mL. To 600 mL of this solution add 100 mL of water, and adjust to pH 1.9 – 2.0 with a solution prepared by adding water to 2.81 g of sodium perchlorate monohydrate to make 1000 mL. To 300 mL of this solution add 200 mL of acetonitrile.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 25	100	0
25 – 55	100 → 0	0 → 100
55 – 60	0	100

Flow rate: 0.8 mL per minute.

System suitability—

Test for required detectability: Pipet 2.5 mL of the standard solution, and add water to make exactly 50 mL. Confirm that the peak area of doripenem obtained with 20 μL of this solution is equivalent to 3.5 to 6.5% of that with 20 μL of the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of doripenem are not less than 15,000 and not more than 1.3, respectively.

System repeatability: When the test is repeated 3 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of doripenem is not more than 0.95%.

Water <*2.48*> 4.0 – 5.0% (0.3 g, volumetric titration, back titration).

Residue on ignition <*2.44*> Not more than 0.1% (1 g).

Assay Weigh accurately amounts of Doripenem Hydrate and Doripenem RS (separately determine the water <*2.48*> in the same manner as Doripenem Hydrate), equivalent to about 25 mg (potency), dissolve each in water to make exactly 200 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of doripenem in each solution.

$$\text{Amount [}\mu\text{g (potency)] of doripenem } (C_{15}H_{24}N_4O_6S_2) = M_S \times A_T/A_S \times 1000$$

M_S: Amount [mg (potency)] of Doripenem RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 300 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: Adjust the pH of 90 mL of 0.02 mol/L potassium dihydrogen phosphate TS to pH 5.6 – 5.7 with a solution prepared by dissolving 3.48 g of dipotassium hydrogen phosphate in water to make 1000 mL. To 100 mL of this solution add water to make exactly 1000 mL. To 970

mL of this solution add 30 mL of acetonitrile.

Flow rate: Adjust so that the retention time of doripenem is about 15 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of doripenem are not less than 5000 and not more than 1.3, respectively.

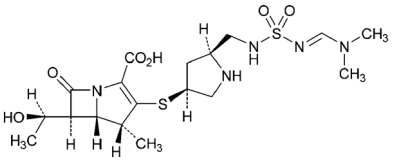
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of doripenem is not more than 1.0%.

Containers and storage Containers—Tight containers.

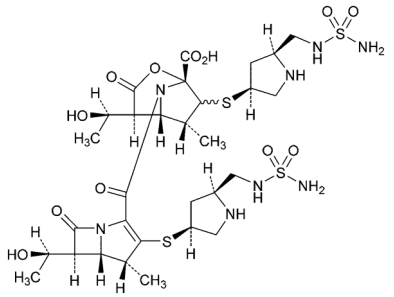
Storage—At a temperature between 2°C and 8°C.

Others

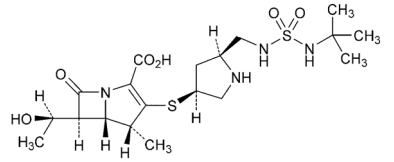
Related substance A:
(4*R*,5*S*,6*S*)-3-{(3*S*,5*S*)-5-[({*N*-(*E*)-(Dimethylamino)methylene]sulfamoyl}amino)methyl]pyrrolidin-3-ylsulfanyl}-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid



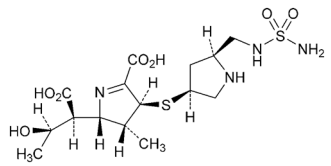
Related substance B:
(1*S*,4*S*,5*S*,6*R*)-4-[(1*R*)-1-Hydroxyethyl]-8-[(4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-{(3*S*,5*S*)-5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carbonyl]-6-methyl-3-oxo-7-{(3*S*,5*S*)-5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl}-2-oxa-8-azabicyclo[3.2.1]octane-1-carboxylic acid



Related substance C:
(4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-({[*N*-(1,1-Dimethylethyl)sulfamoyl]amino}methyl)pyrrolidin-3-ylsulfanyl]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid



Related substance D:
(2*S*,3*R*,4*S*)-2-[(1*S*,2*R*)-1-Carboxy-2-hydroxypropyl]-3-methyl-4-{(3*S*,5*S*)-5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl}-3,4-dihydro-2*H*-pyrrole-5-carboxylic acid



Add the following:

Doripenem for Injection

注射用ドリペネム

Doripenem for Injection is a preparation for injection, which is dissolved before use.

It contains not less than 95.0% and not more than 105.0% of the labeled potency of doripenem ($C_{15}H_{24}N_4O_6S_2$: 420.50).

Method of preparation Prepare as directed under Injections, with Doripenem Hydrate.

Description Doripenem for Injection occurs as a white to pale yellow-brown-white crystalline powder.

Identification Proceed as directed in the Identification (2) under Doripenem Hydrate.

pH ⟨*2.54*⟩ Dissolve an amount of Doripenem for Injection, equivalent to 0.3 g (potency) of Doripenem Hydrate, in 30 mL of water: the pH of the solution is between 4.5 and 6.0.

Purity **(1)** Clarity and color of solution—Dissolve an amount of Doripenem for Injection, equivalent to 0.2 g (potency) of Doripenem Hydrate in 20 mL of water, and proceed as directed in the Purity (1) under Doripenem Hydrate.

(2) Related substances—(i) Dissolve an amount of Doripenem for Injection, equivalent to 20 mg (potency) of Doripenem Hydrate, in 10 mL of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine each peak area by the automatic integration method: the area of the peak other than doripenem and the peak, having the relative retention time of about 2.1 to doripenem, related substance A having the relative retention time of about 2.2, related substance B having the relative retention time of about 2.5 and related substance C having the relative retention time of about 3.2, obtained from the sample solution is not larger than 1/10 times the peak area of doripenem from the standard solution, and the total area of the peaks other than

doripenem and the peak mentioned above from the sample solution is not larger than 1/2 times the peak area of doripenem from the standard solution.

Operating conditions—

Proceed as directed in the operating conditions in the Purity (3) (i) under Doripenem Hydrate.

System suitability—

Test for required detectability: Pipet 2.5 mL of the standard solution, and add water to make exactly 50 mL. Confirm that the peak area of doripenem obtained with 20 μL of this solution is equivalent to 3.5 to 6.5% of that with 20 μL of the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of doripenem are not less than 5000 and not more than 1.3, respectively.

System repeatability: When the test is repeated 3 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of doripenem is not more than 0.95%.

(ii) Dissolve an amount of Doripenem for Injection, equivalent to 20 mg (potency) of Doripenem Hydrate, in 10 mL of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the peak area of related substance D, having the relative retention time of about 0.5 to doripenem, obtained from the sample solution is not larger than the peak area of doripenem from the standard solution.

Operating conditions—

Proceed as directed in the operating conditions in the Purity (3) (ii) under Doripenem Hydrate.

System suitability—

System performance: To 1 mL of the sample solution add 1 mL of 0.1 mol/L hydrochloric acid TS, allow to stand at 25 ± 5°C for 15 minutes, and add water to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, related substance D and doripenem are eluted in this order with the resolution between these peaks being not less than 5. The number of theoretical plates and the symmetry factor of the peak of related substance D are not less than 300 and 0.7 to 1.3, respectively, and those of the peak of doripenem are not less than 5000 and 0.7 to 1.3, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of doripenem is not more than 2.0%.

Water <*2.48*> 4.0 – 5.0% (0.3 g, volumetric titration, back titration).

Bacterial endotoxins <*4.01*> Less than 0.25 EU/mg (potency).

Uniformity of dosage units <*6.02*> It meets the requirement of the Mass variation test.

Foreign insoluble matter <*6.06*> Perform the test according to Method 2: it meets the requirement.

Insoluble particulate matter <*6.07*> It meets the requirement.

Sterility <*4.06*> Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Weigh accurately the mass of the contents of not less than 10 containers of Doripenem for Injection. Weigh accurately an amount of the contents, equivalent to about 25 mg (potency) of Doripenem Hydrate, dissolve in water to make exactly 200 mL, and use this solution as the sample solution. Separately, weigh accurately about 25 mg (potency) of Doripenem RS (separately determine the water <*2.48*> in the same manner as Doripenem Hydrate), dissolve in water to make exactly 200 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay under Doripenem Hydrate.

Amount [μg (potency)] of doripenem ($C_{15}H_{24}N_4O_6S_2$)
$= M_S \times A_T/A_S \times 1000$

M_S: Amount [mg (potency)] of Doripenem RS taken, calculated on the anhydrous basis

Containers and storage Containers—Hermetic containers. Plastic containers for aqueous injections may be used.

Others

Related substances A, B, C and D: Refer to them described in Doripenem Hydrate.

Epirubicin Hydrochloride

エピルビシン塩酸塩

Delete the Purity (4):

Estriol

エストリオール

Change the Description and Optical rotation as follows:

Description Estriol occurs as a white crystalline powder. It is odorless.

It is sparingly soluble in methanol, slightly soluble in ethanol (99.5), and practically insoluble in water.

Optical rotation <*2.49*> $[\alpha]_D^{25}$: +55 – +65° (after drying, 40 mg, ethanol (99.5), 10 mL, 100 mm).

Add the following:

Ethylcellulose

エチルセルロース

[*9004-57-3*]

This monograph is harmonized with the European Pharmacopoeia and the U. S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Ethylcellulose is a partly *O*-ethylated cellulose.

It contains not less than 44.0% and not more than 51.0% of ethoxy group ($-OC_2H_5$: 45.06), calculated on the dried basis.

It may contain a suitable antioxidant.

The viscosity of Ethylcellulose is shown in millipascal second (mPa·s) on the label.

◆**Description** Ethylcellulose occurs as a white to yellowish white, amorphous powder or grains.

It is soluble in dichloromethane.

It forms a slightly white-turbid or white-turbid, viscous liquid upon addition of ethanol (95).

To 1 g of Ethylcellulose add 100 mL of hot water, shake to become turbid, cool to room temperature, and add freshly boiled and cooled water to make 100 mL: the solution is neutral.◆

Identification Spread 2 drops of a solution of Ethylcellulose in dichloromethane (1 in 25) between sodium chloride plates, then remove one of the plates to evaporate the solvent, and determine the infrared absorption spectrum of the plate as directed in the film method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

Viscosity <*2.53*> Weigh exactly a quantity of Ethylcellulose, equivalent to 5.00 g calculated on the dried basis, add 95 g of a mixture of 80 g of toluene and 20 g of ethanol (95), and shake to dissolve. Perform the test with this solution at 25°C as directed in Method I: not less than 80.0% and not more than 120.0% of the labeled viscosity for a nominal viscosity more than 6 mPa·s, and not less than 75.0% and not more than 140.0% of the labeled viscosity for a nominal viscosity not more than 6 mPa·s.

Purity **(1)** Acidity or alkalinity—To 0.5 g of Ethylcellulose add 25 mL of freshly boiled and cooled water, shake for 15 minutes, filter through a glass filter (G3), and use the filtrate as the sample solution. To 10 mL of the sample solution add 0.1 mL of dilute phenolphthalein TS and 0.5 mL of 0.01 mol/L sodium hydroxide VS: a light red color develops. To 10 mL of the sample solution add 0.1 mL of methyl red-sodium hydroxide TS and 0.5 mL of 0.01 mol/L hydrochloric acid VS: a red color develops.

(2) Chloride—Disperse 0.250 g of Ethylcellulose in 50 mL of water, and boil with occasional shaking. Allow to cool, and filter. Discard the first 10 mL of the filtrate, to 10 mL of the subsequent filtrate add water to make 15 mL, and use this solution as the sample solution. Separately, to 10 mL of Standard Chloride Solution add 5 mL of water, and use this solution as the control solution. To 15 mL each of the sample solution and control solution add 1 mL of 2 mol/L nitric acid TS, transfer to test tubes containing 1 mL of a solution of silver nitrate (17 in 1000), allow to stand for 5 minutes protecting from light, and compare the opalescence developed in the both solutions against a black background by viewing transversely: the opalescence developed in the sample solution is not more intense than that of the control solution (not more than 0.1%).

◇**(3)** Heavy metal <*1.07*>—Proceed with 1.0 g of Ethylcellulose according to Method 2, and perform the test. Prepare the control solution with 4.0 mL of Standard Lead Solution (not more than 40 ppm).◇

(4) Acetaldehyde—Introduce 3.0 g of Ethylcellulose into a 250-mL glass-stoppered conical flask, add 10 mL of water, and stir for 1 hour. Allow to stand for 24 hours, filter, add water to the filtrate to make 100 mL, and use this solution as the sample solution. Separately, dissolve 1.0 g of acetaldehyde for assay in water to make 100 mL. To 5 mL of this solution add water to make 500 mL. To 3 mL of this solution add water to make 100 mL, and use this solution as the control solution. Transfer 5 mL each of the sample solution and control solution to 25-mL volumetric flasks, add 5 mL of a solution of 3-methyl-2-benzothiazolonehydrazone hydrochloride monohydrate (1 in 2000), and heat in a water bath at 60°C for 5 minutes. Add 2 mL of iron (III) chloride-amidosulfuric acid TS, and warm again at 60°C for 5 minutes. After cooling, add water to make 25 mL, and compare the color of these solutions: the sample solution is not more intensely colored than the control solution (not more than 100 ppm).

Loss on drying <*2.41*> Not more than 3.0% (1 g, 105°C, 2 hours).

Residue on Ignition <*2.44*> Not more than 0.5% (1 g).

Assay Weigh accurately about 30 mg of Ethylcellulose, transfer to a 5-mL pressure-tight serum vial, add exactly 60 mg of adipic acid, 2 mL of the internal standard solution and 1 mL of hydroiodic acid, seal the vial immediately with a septum coated with fluororesin and an aluminum cap or any other sealing system providing a sufficient air-tightness, and weigh accurately the vial. Take care not to mix the contents in the vial before heating. Place the vial in an oven or heat in a suitable heater with continuous stirring, maintaining an internal temperature of about 115 ± 2°C for 70 min. Allow to cool, and weigh accurately the vial. If the difference of the mass between before heating and after heating is more than 10 mg, prepare a new sample solution. If the

difference of the mass between before heating and after heating is not more than 10 mg, after phase separation, pierce through the septum of the vial with a cooled syringe, and withdraw a sufficient volume of the upper phase as the sample solution. Separately, place exactly 60 mg of adipic acid, 2 mL of the internal standard solution and 1 mL of hydroiodic acid in another serum vial, and seal immediately. Weigh accurately the vial, inject 25 μL of iodoethane for assay through the septum in the vial, and weigh again accurately. Shake thoroughly, after phase separation, pierce through the septum of the vial with a cooled syringe, withdraw a sufficient volume of the upper phase, and use this solution as the standard solution. Perform the test with 1 μL each of the sample solution and standard solution as directed under Gas Chromatography <*2.02*> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of iodoethane to that of the internal standard.

$$\text{Amount (\%) of ethoxy group } (C_2H_5O) = M_S/M_T \times Q_T/Q_S \times 28.89$$

M_S: Amount (mg) of iodoethane for assay taken
M_T: Amount (mg) of Ethylcellulose taken, calculated on the dried basis

Internal standard solution—A solution of *n*-octane in *o*-xylene (1 in 200).

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A fused silica column 0.53 mm in inside diameter and 30 m in length, coated with dimethylpolysiloxane for gas chromatography in 3 μm thickness.

Column temperature: Maintain the temperature at 50°C for 3 minutes, raise to 100°C at a rate of 10°C per minute, then to 250°C at a rate of 35°C per minute, and maintain at 250°C for 8 minutes.

Injection port temperature: A constant temperature of about 250°C.

Detector temperature: A constant temperature of about 280°C.

Carrier gas: Helium.

Flow rate: 4.2 mL per minute (the retention time of the internal standard is about 10 minutes).

Split ratio: 1:40.

System suitability—

System performance: When the procedure is run with 1 μL of the standard solution under the above operating conditions, iodoethane and the internal standard are eluted in this order with the relative retention time of iodoethane to the internal standard being about 0.6, and with the resolution between these peaks being not less than 5.0.

System repeatability: When the test is repeated 6 times with 1 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of iodoethane to that of the internal standard is not more than 2.0%.

◆**Containers and storage** Containers—Well-closed containers.◆

Etizolam

エチゾラム

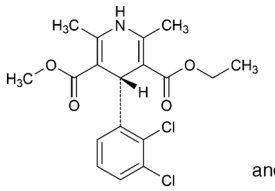
Change the Melting point as follows:

Melting point <*2.60*> 147 – 151°C

Add the following:

Felodipine

フェロジピン



and enantiomer

$C_{18}H_{19}Cl_2NO_4$: 384.25

Ethyl methyl (4*RS*)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

[*72509-76-3*]

Felodipine contains not less than 99.0% and not more than 101.0% of felodipine ($C_{18}H_{19}Cl_2NO_4$), calculated on the dried basis.

Description Felodipine occurs as pale yellow-white to light yellow-white, crystals or crystalline powder.

It is freely soluble in methanol and in ethanol (99.5), and practically insoluble in water.

A solution of Felodipine in methanol (1 in 20) shows no optical rotation.

Identification **(1)** Determine the absorption spectrum of a solution of Felodipine in methanol (1 in 62,500) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Felodipine as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity **(1)** Heavy metals—Being specified separately when the drug is granted approval based on the Law.

(2) Related substances—Dissolve 25 mg of Felodipine in 50 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard

solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic integration method: the area of the peak other than felodipine, related substance B, having the relative retention time of about 0.7 to felodipine, and related substance C, having the relative retention time of about 1.4, obtained from the sample solution is not larger than the peak area of felodipine from the standard solution. Furthermore, the total area of the peaks of related substances B and C from the sample solution is not larger than 10 times the peak area of felodipine from the standard solution, and the total area of the peaks other than felodipine and related substances mentioned above from the sample solution is not larger than 3 times the peak area of felodipine from the standard solution. For this calculation the peak area less than 1/5 times the peak area of felodipine from the standard solution is excluded.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: Dissolve 3.2 g of sodium dihydrogen phosphate dihydrate in 400 mL of water, adjust to pH 3.0 with phosphoric acid, and add 200 mL of methanol and 400 mL of acetonitrile.

Flow rate: Adjust so that the retention time of felodipine is about 12 minutes.

Time span of measurement: About 2 times as long as the retention time of felodipine, beginning after the solvent peak.

System suitability—

Test for required detectability: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the SN ratio of the peak of felodipine is not less than 30.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of felodipine are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of felodipine is not more than 2.0%.

Loss on drying <2.41> Not more than 0.2% (1 g, 105°C, 3 hours).

Residue on ignition <2.44> Not more than 0.1% (1 g).

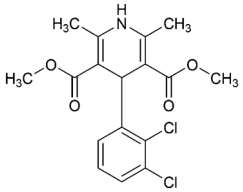
Assay Weigh accurately about 0.16 g of Felodipine, dissolve in 25 mL of t-butyl alcohol and 25 mL of diluted perchloric acid (17 in 200), and titrate <2.50> with 0.1 mol/L cerium (IV) sulfate VS (indicator: 50 μL of 1,10-phenanthroline TS) until the color of the solution changes from orange to colorless. Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L cerium (IV) sulfate VS
= 19.21 mg of $C_{18}H_{19}Cl_2NO_4$

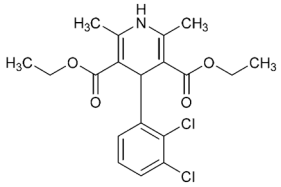
Containers and storage Containers—Well-closed containers.

Others

Related substance B:
Dimethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Related substance C:
Diethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Add the following:

Felodipine Tablets

フェロジピン錠

Felodipine Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$: 384.25).

Method of preparation Prepare as directed under Tablets, with Felodipine.

Identification To a quantity of powdered Felodipine Tablets, equivalent to 4 mg of Felodipine, add 200 mL of methanol, shake thoroughly, add methanol to make 250 mL, and centrifuge. Determine the absorption spectrum of the supernatant liquid as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits maxima between 235 nm and 239 nm, and between 357 nm and 363 nm.

Uniformity of dosage units <6.02> Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

To 1 tablet of Felodipine Tablets add 1 mL of water per 2.5 mg of felodipine ($C_{18}H_{19}Cl_2NO_4$), and shake thoroughly until the tablet is completely disintegrated. Add exactly 1 mL of the internal standard solution per 2.5 mg of felodipine ($C_{18}H_{19}Cl_2NO_4$), and add methanol to make *V* mL so

that each mL contains about 0.25 mg of felodipine ($C_{18}H_{19}Cl_2NO_4$). Centrifuge this solution, filter the supernatant liquid, and use this filtrate as the sample solution. Separately, weigh accurately about 25 mg of felodipine for assay (separately determine the loss on drying <2.41> in the same conditions as Felodipine), add 10 mL of water, and add exactly 10 mL of the internal standard solution. Add methanol to make 100 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay.

Amount (mg) of felodipine ($C_{18}H_{19}Cl_2NO_4$)
$= M_S \times Q_T/Q_S \times V/100$

M_S: Amount (mg) of felodipine for assay taken, calculated on the dried basis

Internal standard solution—A solution of butyl parahydroxybenzoate in methanol (1 in 3000).

Dissolution <6.10> When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of a solution prepared by dissolving 1 g of polysorbate 80 in water to make 5000 mL, as the dissolution medium, the dissolution rates in 45 minutes of a 2.5-mg tablet and a 5-mg tablet are not less than 80% and not less than 75%, respectively.

Start the test with 1 tablet of Felodipine Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 10 mL of the first filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL so that each mL contains about 2.8 μg of felodipine ($C_{18}H_{19}Cl_2NO_4$), and use this solution as the sample solution. Separately, weigh accurately about 28 mg of felodipine for assay (separately determine the loss on drying <2.41> in the same conditions as Felodipine), and dissolve in methanol to make exactly 200 mL. Pipet 2 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 50 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of felodipine in each solution.

Dissolution rate (%) with respect to the labeled amount of felodipine ($C_{18}H_{19}Cl_2NO_4$)
$= M_S \times A_T/A_S \times V'/V \times 1/C \times 9$

M_S: Amount (mg) of felodipine for assay taken, calculated on the dried basis
C: Labeled amount (mg) of felodipine ($C_{18}H_{19}Cl_2NO_4$) in 1 tablet

Operating conditions—

Column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

System suitability—

System performance: When the procedure is run with 50 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of felodipine are not less than 3000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 50 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of felodipine is not more than 2.0%.

Assay Weigh accurately the mass of not less than 20 Felodipine Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 10 mg of felodipine ($C_{18}H_{19}Cl_2NO_4$), add 20 mL of water, add exactly 4 mL of the internal standard solution, add methanol to make 100 mL and shake. Centrifuge this solution, filter the supernatant liquid through a membrane filter with a pore size not exceeding 0.45 μm, and use the filtrate as the sample solution. Separately, weigh accurately about 10 mg of felodipine for assay (separately determine the loss on drying <2.41> in the same conditions as Felodipine), add 20 mL of water, add exactly 4 mL of the internal standard solution, add methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of felidipine to that of the internal standard.

Amount (mg) of felodipine ($C_{18}H_{19}Cl_2NO_4$) $= M_S \times Q_T/Q_S$

M_S: Amount (mg) of felodipine for assay taken, calculated on the dried basis

Internal standard solution—A solution of butyl parahydroxybenzoate in methanol (1 in 6000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 264 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of methanol, water, a solution of sodium perchlorate monohydrate (281 in 2000) and diluted perchloric acid (17 in 200) (65:25:8:2).

Flow rate: Adjust so that the retention time of felodipine is about 12 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the internal standard and felodipine are eluted in this order with the resolution between these peaks being not less than 5.

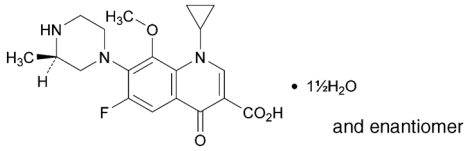
System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of felodipine is not more than 1.0%.

Containers and storage Containers—Tight containers.

Add the following:

Gatifloxacin Hydrate

ガチフロキサシン水和物



$C_{19}H_{22}FN_3O_4.1½H_2O$: 402.42

1-Cyclopropyl-6-fluoro-8-methoxy-7-[(3*RS*)-3-methylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid sesquihydrate

[*180200-66-2*]

Gatifloxacin Hydrate contains not less than 98.5% and not more than 101.5% of gatifloxacin ($C_{19}H_{22}FN_3O_4$: 375.39), calculated on the anhydrous basis.

Description Gatifloxacin Hydrate occurs as white to pale yellow, crystals or crystalline powder.

It is slightly soluble in methanol and in ethanol (99.5), and very slightly soluble in water.

It dissolves in sodium hydroxide TS.

It is gradually colored to pale yellow by light.

A solution of Gatifloxacin Hydrate in dilute sodium hydroxide TS (1 in 100) shows no optical rotation.

Identification **(1)** Determine the absorption spectrum of a solution of Gatifloxacin Hydrate in dilute sodium hydroxide TS (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Gatifloxacin RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Gatifloxacin Hydrate as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum or the spectrum of Gatifloxacin RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity **(1)** Clarity and color of solution—Dissolve 1.0 g of Gatifloxacin Hydrate in 10 mL of sodium hydroxide TS: the solution is clear. Perform the test with the solution as directed under Methods for Color Matching <*2.65*>: the solution is not more colored than diluted Matching Fluid O (1 in 5).

(2) Heavy metals <*1.07*>—Proceed with 1.0 g of Gatifloxacin Hydrate according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Related substances—Dissolve 20 mg of Gatifloxacin Hydrate in 50 mL of the dissolving solution, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the dissolving solution to make exactly 100 mL. Pipet 2 mL of this solution, add the dissolving solution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the peak area of the related substance A, having the relative retention time of about 1.2 to gatifloxacin, obtained from the sample solution is not larger than 2 times the peak area of gatifloxacin from the standard solution, and the area of the peak other than gatifloxacin and the peak mentioned above from the sample solution is not larger than the peak area of gatifloxacin from the standard solution. Furthermore, the total area of the peaks other than gatifloxacin from the sample solution is not larger than 3 times the peak area of gatifloxacin from the standard solution.

Dissolving solution: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (4:1).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 325 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35°C.

Mobile phase A: A mixture of diluted triethylamine (1 in 100), adjusted to pH 4.3 with phosphoric acid, and acetonitrile (22:3).

Mobile phase B: A mixture of diluted triethylamine (1 in 100), adjusted to pH 4.3 with phosphoric acid, and acetonitrile (1:1).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 15	100	0
15 – 30	100 → 0	0 → 100
30 – 40	0	100

Flow rate: 1.0 mL per minute (the retention time of gatifloxacin is about 16 minutes).

Time span of measurement: About 2.5 times as long as the retention time of gatifloxacin, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 5 mL of the standard solution, and add the dissolving solution to make exactly 10 mL. Confirm that the peak area of gatifloxacin ob-

tained with 20 μL of this solution is equivalent to 40 to 60% of that with 20 μL of the standard solution.

System performance: Dissolve 20 mg of methyl 4-aminobenzoate in 50 mL of the dissolving solution. To 5 mL of this solution add 1 mL of the sample solution and the dissolving solution to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, gatifloxacin and methyl 4-aminobenzoate are eluted in this order with the resolution between these peaks being not less than 4.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of gatifloxacin is not more than 3.0%.

Water ⟨*2.48*⟩ 6.0 – 9.0% (0.1 g, volumetric titration, direct titration).

Residue on ignition ⟨*2.44*⟩ Not more than 0.1% (1 g).

Assay Weigh accurately about 50 mg of Gatifloxacin Hydrate and Gatifloxacin RS (separately determine the water ⟨*2.48*⟩ in the same manner as Gatifloxacin Hydrate), and dissolve each in the dissolving solution to make exactly 100 mL. Pipet 2 mL each of these solution, add exactly 2 mL of the internal standard solution to them, add the dissolving solution to make 25 mL, and use these solutions as the sample solution and standard solutions. Perform the test with 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of gatifloxacin to that of the internal standard.

$$\text{Amount (mg) of gatifloxacin } (C_{19}H_{22}FN_3O_4) = M_S \times Q_T/Q_S$$

M_S: Amount (mg) of Gatifloxacin RS taken, calculated on the anhydrous basis

Internal standard solution—A solution of methyl 4-aminobenzoate in the dissolving solution (1 in 4000).

Dissolving solution: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (4:1).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4 mm in inside diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of diluted triethylamine (1 in 100), adjusted to pH 4.5 with phosphoric acid, and acetonitrile (87:13).

Flow rate: Adjust so that the retention time of gatifloxacin is about 5 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, gatifloxacin and the internal standard are eluted in this order with the resolution between these peaks being not less than 4.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of gatifloxacin to that of the internal standard is not more than 1.0%.

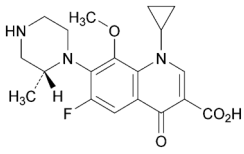
Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Others

Related substance A:

1-Cyclopropyl-6-fluoro-8-methoxy-7-[(2*RS*)-2-methylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



and enantiomer

Add the following:

Gatifloxacin Ophthalmic Solution

ガチフロキサシン点眼液

Gatifloxacin Ophthalmic Solution is an aqueous ophthalmic preparation.

It contains not less than 95.0% and not more than 107.0% of the labeled amount of gatifloxacin ($C_{19}H_{22}FN_3O_4$: 375.39).

Method of preparation Prepare as directed under Ophthalmic Liquids and Solutions, with Gatifloxacin Hydrate.

Description Gatifloxacin Ophthalmic Solution is a clear, pale yellow liquid.

Identification To a volume of Gatifloxacin Ophthalmic Solution, equivalent to 6 mg of gatifloxacin ($C_{19}H_{22}FN_3O_4$), add diluted sodium hydroxide TS (1 in 10) to make 30 mL. To 1 mL of this solution add diluted sodium hydroxide TS (1 in 10) to make 20 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩: it exhibits maxima between 238 nm and 242 nm, between 287 nm and 291 nm, and between 336 nm and 340 nm.

Osmotic pressure ratio Being specified separately when the drug is granted approval based on the Law.

pH Being specified separately when the drug is granted approval based on the Law.

Purity Related substance—To a volume of Gatifloxacin Ophthalmic Solution, equivalent to 6 mg of gatifloxacin ($C_{19}H_{22}FN_3O_4$), add the diluting solution to make 30 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the diluting solution to make exactly 100 mL. Pipet 2 mL of this solution, add the diluting

solution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 40 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions. Determine each peak area by the automatic integration method: the peak area of the related substance A, having the relative retention time of about 1.2 to gatifloxacin, obtained from the sample solution is not larger than 2 times the peak area of gatifloxacin from the standard solution, and the area of the peak other than gatifloxacin and the peak mentioned above from the sample solution is not larger than the peak area of gatifloxacin from the standard solution. Furthermore, the total area of the peaks other than gatifloxacin from the sample solution is not larger than 3 times the peak area of gatifloxacin from the standard solution.

Diluting solution: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (4:1).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 325 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase A: A mixture of diluted triethylamine (1 in 100) and acetonitrile (22:3), adjusted to pH 4.3 with phosphoric acid.

Mobile phase B: A mixture of diluted triethylamine (1 in 100) and acetonitrile (1:1), adjusted to pH 4.3 with phosphoric acid.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 15	100	0
15 – 30	100 → 0	0 → 100
30 – 40	0	100

Flow rate: 0.9 mL per minute (the retention time of gatifloxacin is about 16 minutes).

Time span of measurement: For 40 minutes after injection, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 5 mL of the standard solution, and add the diluting solution to make exactly 10 mL. Confirm that the peak area of gatifloxacin obtained with 40 μL of this solution is equivalent to 40 to 60% of that with 40 μL of the standard solution.

System performance: Dissolve 20 mg of methyl 4-aminobenzoate in 100 mL of the diluting solution. To 5 mL of this solution and 1 mL of the sample solution add the diluting solution to make 100 mL. When the procedure is run with 40 μL of this solution under the above operating conditions, gatifloxacin and methyl 4-aminobenzoate are eluted in this order with the resolution between these peaks being not less than 4.

System repeatability: When the test is repeated 6 times with 40 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of gatifloxacin is not more than 3.0%.

Foreign insoluble matter ⟨*6.11*⟩ It meets the requirement.

Insoluble particulate matter ⟨*6.08*⟩ It meets the requirement.

Sterility ⟨*4.06*⟩ Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Pipet a volume of Gatifloxacin Ophthalmic Solution, equivalent to about 6 mg of gatifloxacin ($C_{19}H_{22}FN_3O_4$), and add the diluting solution to make exactly 30 mL. Pipet 2 mL of this solution, add exactly 3 mL of the internal standard solution, add the diluting solution to make 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 22 mg of Gatifloxacin RS (separately determine the water ⟨*2.48*⟩ in the same manner as Gatifloxacin Hydrate), and dissolve in the diluting solution to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 3 mL of the internal standard solution, add the diluting solution to make 20 mL, and use this solutions as the standard solution. Perform the test with 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of gatifloxacin to that of the internal standard.

$$\text{Amount (mg) of gatifloxacin } (C_{19}H_{22}FN_3O_4) = M_S \times Q_T/Q_S \times 3/10$$

M_S: Amount (mg) of Gatifloxacin RS taken, calculated on the anhydrous basis

Internal standard solution—A solution of methyl 4-aminobenzoate in the diluting solution (1 in 10,000).

Diluting solution: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (4:1).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of water, acetonitrile and triethylamine (81:18:1), adjusted to pH 4.5 with phosphoric acid.

Flow rate: Adjust so that the retention time of gatifloxacin is about 6 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, gatifloxacin and the internal standard are eluted in this order with the resolution between these peaks being not less than 10.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of gatifloxacin to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Others

Related substances A: Refer to it described in Gatifloxacin Hydrate.

Add the following:

Gentamicin Sulfate Injection

ゲンタマイシン硫酸塩注射液

Gentamicin Sulfate Injection is an aqueous injection.

It contains not less than 90.0% and not more than 110.0% of the labeled potency of gentamicin C_1 ($C_{21}H_{43}N_5O_7$: 477.60).

Method of preparation Prepare as directed under Injections, with Gentamicin Sulfate.

Description Gentamicin Sulfate Injection is a clear and colorless liquid.

Identification To a volume of Gentamicin Sulfate Injection, equivalent to 40 mg (potency) of Gentamicin Sulfate, add water to make 10 mL, and use this solution as the sample solution. Separately, dissolve an amount of Gentamicin Sulfate RS, equivalent to 20 mg (potency), in 5 mL of water, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with the lower layer of a mixture of chloroform, ammonia solution (28) and methanol (2:1:1) to a distance of about 15 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-water saturated 1-butanol TS on the plate, and heat the plate at 100°C for 10 minutes: three principal spots obtained from the sample solution are the same with the corresponding spots from the standard solution in color tone and the *R*f value, respectively.

Osmotic pressure ratio Being specified separately when the drug is granted approval based on the Law.

pH <*2.54*> 4.0 – 6.0

Bacterial endotoxins <*4.01*> Less than 0.50 EU/mg (potency).

Extractable volume <*6.05*> It meets the requirement.

Foreign insoluble matter <*6.06*> Perform the test according to Method 1: it meets the requirement.

Insoluble particulate matter <*6.07*> It meets the requirement.

Sterility <*4.06*> Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Perform the test according to the Cylinder-plate method as directed under Microbial Assay for Antibiotics <*4.02*> according to the following conditions.

(i) Test organism, agar media for base and seed layer, agar medium for transferring test organisms, and standard solutions—Proceed as directed in the Assay under Gentamicin Sulfate.

(ii) Sample solutions—Pipet a volume of Gentamicin Sulfate Injection, equivalent to about 40 mg (potency) of Gentamicin Sulfate, add 0.1 mol/L phosphate buffer solution (pH 8.0) to make exactly 200 mL. Pipet a suitable volume of this solution, add 0.1 mol/L phosphate buffer solution (pH 8.0) to make solutions so that each mL contains 4 μg (potency) and 1 μg (potency), and use these solutions as the high concentration sample solution and the low concentration sample solution, respectively.

Containers and storage Containers—Hermetic containers.

Add the following:

Gentamicin Sulfate Ointment

ゲンタマイシン硫酸塩軟膏

Gentamicin Sulfate Ointment contains not less than 90.0% and not more than 110.0% of the labeled potency of gentamicin C_1 ($C_{21}H_{43}N_5O_7$: 477.60).

Method of preparation Prepare as directed under Ointments, with Gentamicin Sulfate.

Identification To an amount of Gentamicin Sulfate Ointment, equivalent to 5 mg (potency) of Gentamicin Sulfate, add 10 mL of diethyl ether, and shake in lukewarm water, if necessary, to dissolve. Add 5 mL of water, shake for 10 minutes, centrifuge, and use the water layer as the sample solution. Separately, dissolve an amount of Gentamicin Sulfate RS, equivalent to 10 mg (potency), in 10 mL of water, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with the lower layer of a mixture of chloroform, ammonia solution (28) and methanol (2:1:1) to a distance of about 15 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-water saturated 1-butanol TS on the plate, and heat the plate at 100°C for 10

minutes: three principal spots obtained from the sample solution are the same with the corresponding spots from the standard solution in color tone and the *R*f value, respectively.

Assay Perform the test according to the Cylinder-plate method as directed under Microbial Assay for Antibiotics <*4.02*> according to the following conditions.

(i) Test organism, agar media for base and seed layer, agar medium for transferring test organisms, and standard solutions—Proceed as directed in the Assay under Gentamicin Sulfate.

(ii) Sample solutions—Weigh accurately an amount of Gentamicin Sulfate Ointment, equivalent to about 1 mg (potency) of Gentamicin Sulfate, transfer to a separator, add 50 mL of diethyl ether, and shake until the solution becomes uniform. Add 25 mL of 0.1 mol/L phosphate buffer solution (pH 8.0), shake, and collect the water layer. Repeat the same procedure with 25 mL of 0.1 mol/L phosphate buffer solution (pH 8.0), and combine the water layers. To this solution add 0.1 mol/L phosphate buffer solution (pH 8.0) to make exactly 100 mL. Pipet a suitable volume of this solution, add 0.1 mol/L phosphate buffer solution (pH 8.0) to make solutions so that each mL contains 4 μg (potency) and 1 μg (potency), and use these solutions as the high concentration sample solution and the low concentration sample solution, respectively.

Containers and storage Containers—Tight containers.

Delete the following Monograph:

Adsorbed Habu-venom Toxoid

沈降はぶトキソイド

Haloperidol

ハロペリドール

Change the Melting point as follows:

Melting point <*2.60*> 150 – 154°C

Hydrocortisone

ヒドロコルチゾン

Change the Description and Optical rotation as follows:

Description Hydrocortisone occurs as a white crystalline powder.

It is sparingly soluble in methanol and in ethanol (99.5), and very slightly soluble in water.

Melting point: 212 – 220°C (with decomposition).

It shows crystal polymorphism.

Optical rotation <*2.49*> $[\alpha]_D^{25}$: +160 – +170° (after drying, 0.1 g, ethanol (99.5), 10 mL, 100 mm).

Hydrocortisone Acetate

ヒドロコルチゾン酢酸エステル

Change the Description and Optical rotation as follows:

Description Hydrocortisone Acetate occurs as white, crystals or crystalline powder.

It is freely soluble in dimethylsulfoxide, slightly soluble in methanol and in ethanol (95), and practically insoluble in water.

Melting point: about 220°C (with decomposition).

It shows crystal polymorphism.

Optical rotation <*2.49*> $[\alpha]_D^{25}$: +154 – +164° (after drying, 50 mg, dimethylsulfoxide, 10 mL, 100 mm).

Hydrocortisone and Diphenhydramine Ointment

ヒドロコルチゾン·ジフェンヒドラミン軟膏

Change the Identification (3) as follows:

Identification

(3) To 0.2 g of Hydrocortisone and Diphenhydramine Ointment add 0.5 mL of methanol, warm, and shake. After cooling, separate the methanol layer, and use this layer as the sample solution. Dissolve 10 mg each of hydrocortisone acetate and diphenhydramine in 10 mL each of methanol, and use these solutions as standard solutions (1) and (2). Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solutions (1) and (2) on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and diethyl ether (4:1) to a distance of about 5 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): two spots obtained from the sample solution show the same *R*f value as the corresponding spots from standard solutions (1) and (2).

Add the following:

Hydroxyethylcellulose

ヒドロキシエチルセルロース

[*9004-62-0*]

This monograph is harmonized with the European Pharmacopoeia and the U. S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Hydroxyethylcellulose is partly *O*-(2-hydroxyethylated) cellulose.

It contains not less than 30.0% and not more than 70.0% of hydroxyethoxy group (-OC_2H_4OH: 61.06), calculated on the dried basis.

It may contain suitable pH-adjusting agents such as phosphates.

◆The viscosity is shown in millipascal second (mPa·s) on the label.◆

◆**Description** Hydroxyethylcellulose occurs as a white to yellowish white, powder or grains.

It is practically insoluble in ethanol (95).

It forms a viscous liquid upon addition of water.

It is hygroscopic.◆

Identification **(1)** Determine the infrared absorption spectrum of Hydroxyethylcellulose as directed in the ATR method under Infrared Spectrophotometry <*2.25*> and compare the spectrum with the spectrum of Hydroxyethylcellulose RS for Identification: both spectra exhibit similar intensities of absorption at the same wave numbers.

(2) Disperse 1.0 g of Hydroxyethylcellulose, calculated on the dried basis, in 50 mL of freshly boiled and cooled water. After 10 minutes, add freshly boiled and cooled water to make 100 mL, stir to dissolve completely, and use this solution as the sample solution. Boil 10 mL of the sample solution: the solution is clear.

◆**Viscosity** <*2.53*> Weigh exactly a quantity of Hydroxyethylcellulose, equivalent to 10.00 g calculated on the dried basis, add 400 mL of water, stir to dissolve, and add water to make exactly 500.0 g. Remove air bubbles, and use this solution as the sample solution. Perform the test with the sample solution at 20 ± 0.1°C as directed in Method II under Viscosity Determination, using a beaker with an inside diameter of not less than 70 mm and a single cylinder-type rotational viscometer, according to the following operating conditions: not less than 75% and not more than 140% of the labeled viscosity.

Operating conditions—

Apparatus: Brookfield type viscometer LV or RV model.

Rotor No., rotation frequency and calculation multiplier: According to the following table, depending on the labeled viscosity.

Labeled viscosity (mPa·s)				Model	Rotor No.	Rotation frequency /min	Calculation multiplier
		less than 200		LV	1	30	2
Not less than 200 and less than 4000				LV	3	30	40
〃	4000	〃	10,000	LV	4	30	200
〃	10,000	〃	50,000	RV	6	20	500
〃	50,000			RV	7	20	2000

Procedure of apparatus: Read a value after 2 minutes of rotation, and stop the rotation for at least 2 minutes. Repeat this procedure more two times, and average the three observed values.◆

pH <*2.54*> The pH of the sample solution obtained in the Identification (2) is between 5.5 and 8.5.

Purity **(1)** Chloride—To 1 mL of the sample solution obtained in the Identification (2) add water to make 30 mL, and use this solution as the sample solution. Separately, to 10 mL of Standard Chloride Solution add 5 mL of water, and use this solution as the control solution. To 15 mL each of the sample solution and control solution add 1 mL of diluted nitric acid (1 in 5), transfer to test tubes containing 1 mL of a solution of silver nitrate (17 in 1000), allow to stand for 5 minutes protecting from light, and compare the opalescence developed in the both solutions against a black background by viewing transversely: the opalescence developed in the sample solution is not more intense than that of the control solution (not more than 1.0%).

(2) Nitrate—Prepare the solutions before use. Dissolve 0.50 g of Hydroxyethylcellulose in the diluting solution to make exactly 100 mL, and use this solution as the sample solution. Separately, dissolve 0.8154 g of potassium nitrate in the diluting solution to make 1000 mL, and use this solution as the standard nitrate stock solution. If the viscosity of Hydroxyethylcellulose is not more than 1000 mPa·s, pipet 10 mL, 20 mL and 40 mL of the standard nitrate stock solution, add the diluting solution to each to make exactly 100 mL, and use these solutions as the standard solutions. If the viscosity of Hydroxyethylcellulose is more than 1000 mPa·s, pipet 1 mL, 2 mL and 4 mL of the standard nitrate stock solution, add the diluting solution to each to make exactly 100 mL, and use these solutions as the standard solutions. Perform the test with the sample solution and standard solutions using a nitrate-selective electrode as an indicator electrode, a silver-silver chloride electrode as a reference electrode and diluted ammonium sulfate TS (1 in 30) as reference electrolyte. Calculate the concentration of nitrates in the sample solution using a calibration curve obtained from the potential differences of the standard solutions: not more than 3.0%, calculated on the dried basis, if Hydroxyethylcellulose has a viscosity of not more than 1000 mPa·s, and not more than 0.2%, calculated on the dried basis, if Hydroxyethylcellulose has a viscosity of more than 1000 mPa·s.

Diluting solution: To a mixture of 50 mL of 1 mol/L sulfuric acid TS and 800 mL of water add 135 g of potassium

dihydrogen phosphate, and add water to make 1000 mL. To this solution add water to make exactly 25 times the initial volume.

In order to determine the applicable limit, determine the viscosity using the following procedure.

Introduce a quantity of Hydroxyethylcellulose, equivalent to 2.00 g calculated on the dried basis, into 50 g of water, stir, add water to make 100 g, and stir to dissolve completely. Determine the viscosity using a rotating viscometer at 25°C and at a shear rate of 100 s^{-1} for substances with an expected viscosity less than 100 mPa·s, at a shear rate of 10 s^{-1} for substances with an expected viscosity not less than 100 mPa·s and not more than 20,000 mPa·s, and at a shear rate of 1 s^{-1} for substances with an expected viscosity more than 20,000 mPa·s. If it is impossible to obtain a shear rate of exactly 10 s^{-1} or 100 s^{-1} respectively, use a rate slightly higher and a rate slightly lower and interpolate.

◇**(3)** Heavy metal <*1.07*>—Proceed with 1.0 g of Hydroxyethylcellulose according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).◇

(4) Aldehydes—Introduce 1.0 g of Hydroxyethylcellulose into a glass-stoppered test tube, add 10 mL of ethanol (99.5), stopper the tube tightly, and stir for 30 minutes. Centrifuge, and use the supernatant liquid as the sample solution. Use Standard Glyoxal Solution as the control solution. Pipet 2 mL each of the sample solution and control solution, to each add 5 mL of a solution prepared by dissolving 4 g of 3-methyl-2-benzothiazolonehydrazone hydrochloride monohydrate in diluted acetic acid (100) (4 in 5) to make 1000 mL, shake to homogenize, and allow to stand for 2 hours. Compare the color of these solutions: the sample solution is not more intensely colored than the control solution (not more than 20 ppm).

Loss on drying <*2.41*> Not more than 10.0% (1 g, 105°C, 3 hours).

Residue on Ignition <*2.44*> Not more than 4.0% if the viscosity of Hydroxyethylcellulose is not more than 1000 mPa·s, and not more than 1.0% if the viscosity of Hydroxyethylcellulose is more than 1000 mPa·s (1 g). In order to determine the applicable limit, determine the viscosity according to the method in the Purity (2).

Assay Weigh accurately about 30 mg of Hydroxyethylcellulose, transfer to a 5-mL pressure-tight serum vial, add exactly 60 mg of adipic acid, 2 mL of the internal standard solution and 1 mL of hydroiodic acid, seal the vial immediately with a septum coated with fluororesin and an aluminum cap or any other sealing system providing a sufficient air-tightness, and weigh accurately the vial. Take care not to mix the content of the vial before heating. Place the vial in an oven or heat in a suitable heater with continuous stirring, maintaining the internal temperature of about 165 ± 2°C for 2.5 hours. Allow to cool and weigh accurately the vial. If the difference of the mass between before heating and after heating is more than 10 mg, prepare a new sample solution. If the difference of the mass between before heating and after heating is not more than 10 mg, after phase separation, pierce through the septum of the vial with a cooled syringe, and withdraw a sufficient volume of the upper phase as the sample solution. Separately, place exactly 60 mg of adipic acid, 2 mL of the internal standard solution and 1 mL of hydroiodic acid in another serum vial, and seal immediately. Weigh accurately the vial, inject 55 μL of iodoethane for assay through the septum in the vial, and weigh again accurately. Shake thoroughly, after phase separation, pierce through the septum of the vial with a cooled syringe, and withdraw a sufficient volume of the upper phase as the standard solution. Perform the test with 1 μL each of the sample solution and standard solution as directed under Gas Chromatography <*2.02*> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of iodoethane to that of the internal standard.

$$\text{Amount (\%) of hydroethoxy group } (C_2H_5O_2) = M_S/M_T \times Q_T/Q_S \times 39.15$$

M_S: Amount (mg) of iodoethane for assay taken

M_T: Amount (mg) of Hydroxyethylcellulose taken, calculated on the dried basis

Internal standard solution—A solution of *n*-octane in *o*-xylene (1 in 200).

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A fused silica column 0.53 mm in inside diameter and 30 m in length, coated with dimethylpolysiloxane for gas chromatography in 3 μm thickness.

Column temperature: Maintain the temperature at 50°C for 3 minutes, raise to 100°C at a rate of 10°C per minute, then raise to 250°C at a rate of 35°C per minute, and maintain at 250°C for 8 minutes.

Injection port temperature: A constant temperature of about 250°C.

Detector temperature: A constant temperature of about 280°C.

Carrier gas: Helium.

Flow rate: 4.2 mL per minutes (the retention time of the internal standard is about 10 minutes).

Split ratio: 1:40.

System suitability—

System performance: When the procedure is run with 1 μL of the standard solution under the above operating conditions, iodoethane and the internal standard are eluted in this order with the relative retention time of iodoethane to the internal standard being about 0.6 and the resolution between these peaks being not less than 5.0.

System repeatability: When the test is repeated 6 times with 1 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of iodoethane to that of the internal standard is not more than 2.0%.

◆**Containers and storage** Containers—Tight containers.◆

Change the following as follows:

Hydroxypropylcellulose

ヒドロキシプロピルセルロース

[*9004-64-2*]

This monograph is harmonized with the European Pharmacopoeia and the U. S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Hydroxypropylcellulose is partially *O*-(2-hydroxypropylated) cellulose.

It contains not less than 53.4% and not more than 80.5% of hydroxypropoxy group ($-OC_3H_6OH$: 75.09), calculated on the dried basis.

It may contain silicon dioxide as anti-caking agent.

◆The label states the addition in the case where silicon dioxide is added as anti-caking agent.◆

◆**Description** Hydroxypropylcellulose occurs as a white to yellowish white powder.

It forms a viscous liquid upon addition of water or ethanol (95).◆

Identification **(1)** Dissolve 1 g of Hydroxypropylcellulose in 100 mL of water, transfer 1 mL of the solution to a glass plate, and allow the water to evaporate: a thin film is formed.

(2) Determine the infrared absorption spectrum of Hydroxypropylcellulose as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers. If there are an absorption at about 1719 cm^{-1}, disregard the absorption.

pH <*2.54*> Disperse evenly 1.0 g of Hydroxypropylcellulose in 100 mL of freshly boiled water, and allow to cool the mixture while stirring with a magnetic stirrer: the pH of the solution is between 5.0 and 8.0.

Purity

◇**(1)** Heavy metals<*1.07*>—Proceed with 1.0 g of Hydroxypropylcellulose according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).◇

(2) Silicon dioxide—Apply to Hydroxypropylcellulose, if the addition of silicon dioxide is stated on the label and if more than 0.2% residue is found in the Residue on ignition test. Weigh accurately the crucible containing the residue tested in the Residue on ignition of Hydroxypropylcellulose (*a* (g)). Moisten the residue with water, and add 5 mL of hydrofluoric acid, in small portions. Evaporate it on a steam bath to dryness and cool. Add 5 mL of hydrofluoric acid and 0.5 mL of sulfuric acid, and evaporate to dryness. Slowly increase the temperature until all the acids have been volatilized, and ignite at 1000 ± 25°C. Cool the crucible in a desiccator, and weigh (*b* (g)). Calculate the amount of silicon dioxide by the following equation: not more than 0.6%.

$$\text{Amount (\%) of silicon dioxide } (SiO_2) = (a - b)/M \times 100$$

M: Amount (g) of Hydroxypropylcellulose used for residue on ignition test

Loss on drying <*2.41*> Not more than 5.0% (1 g, 105°C, 4 hours).

Residue on ignition <*2.44*> Not more than 0.8% (1 g, platinum crucible).

Assay Weigh accurately about 30 mg of Hydroxypropylcellulose, transfer to a reaction vial, add exactly 60 mg of adipic acid, 2 mL of the internal standard solution and 1 mL of hydriodic acid, stopper the vial tightly, and weigh accurately. Place the vial in an oven or heat by a suitable heater with continuous stirring, maintaining the internal temperature of 115 ± 2°C for 70 minutes. Allow the vial to cool and weigh accurately. If the difference of the mass between before heating and after heating is more than 10 mg, prepare a new test solution. If the difference of the mass between before heating and after heating is not more than 10 mg, after phase separation by allowing the vial to stand, pierce through the septum of the vial with a cooled syringe, and withdraw a sufficient volume of the upper phase as the sample solution. Separately, place exactly 60 mg of adipic acid, 2 mL of internal standard solution and 1 mL of hydriodic acid in an another reaction vial, stopper tightly, and weigh accurately. Inject 25 μL of isopropyl iodide for assay through the septum, and again weigh accurately. Shake the vial thoroughly, and after phase separation by allowing the vial to stand, pierce through the septum of the vial with a cooled syringe, and withdraw a sufficient volume of the upper phase as the standard solution. Perform the test with 2 μL each of the sample solution and standard solution as directed under Gas Chromatography <*2.02*> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of isopropyl iodide to that of the internal standard.

$$\text{Amount (\%) of hydroxypropoxy group } (C_3H_7O_2) = M_S/M_T \times Q_T/Q_S \times 1.15 \times 44.17$$

M_S: Amount (mg) of isopropyl iodide for assay taken
M_T: Amount (mg) of Hydroxypropylcellulose taken, calculated on the dried basis
1.15: Correction factor

Internal standard solution—A solution of methylcyclohexan in *o*-xylene (1 in 50).

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A fused silica tube 0.53 mm in diameter and 30

m in length, coated with methylsilicone polymer for gas chromatography in 3 μm thickness.

Column Temperature: Maintain the temperature at 40°C for 3 minutes, raise to 100°C at a rate of 10°C per minute, then raise to 250°C at a rate of 50°C per minute, and maintain at 250°C for 3 minutes.

Injection port temperature: A constant temperature of about 180°C.

Detector temperature: A constant temperature of about 280°C.

Carrier gas: Helium.

Flow rate: 52 cm per second (the retention time of the internal standard is about 8 minutes).

Split ratio: 1:50.

System suitability—

System performance: When the procedure is run with 2 μL of the standard solution under the above operating conditions, isopropyl iodide and the internal standard are eluted in this order with the relative retention time of isopropyl iodide to the internal standard being about 0.8, and with the resolution between these peaks being not less than 2.0.

System repeatability: When the test is repeated 6 times with 2 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of isopropyl iodide to that of the internal standard is not more than 2.0%.

◆**Containers and storage** Containers—Well-closed containers.◆

Change the following as follows:

Hypromellose

ヒプロメロース

[*9004-65-3*]

This monograph is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Hypromellose is a methyl and hydroxypropyl mixed ether of cellulose.

There are four substitution types of Hypromellose, 1828, 2208, 2906 and 2910. They contain methoxy ($-OCH_3$: 31.03) and hydroxypropoxy ($-OC_3H_6OH$: 75.09) groups conforming to the limits for the types of Hypromellose shown in the table below, calculated on the dried basis.

The viscosity is shown in millipascal second (mPa·s) on the label, together with the substitution type.

Substitution Type	Methoxy Group (%)		Hydroxypropoxy Group (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

◆**Description** Hypromellose occurs as a white to yellowish white, powder or grains.

It is practically insoluble in ethanol (99.5).

It swells with water and becomes a clear or slightly turbid, viscous solution.◆

Identification **(1)** Disperse evenly 1.0 g of Hypromellose over the surface of 100 mL of water in a beaker, while gently tapping the top of the beaker, if necessary, and allow the beaker to stand: it aggregates on the surface of water.

(2) Add 1.0 g of Hypromellose to 100 mL of hot water, and stir: it becomes a suspension. Cool the suspension to 10°C, and stir: the resulting liquid is a clear or a slightly cloudy, viscous fluid.

(3) To 0.1 mL of the viscous fluid obtained in (2) add 9 mL of diluted sulfuric acid (9 in 10), shake, heat in a water bath for exactly 3 minutes, and immediately cool in ice water. Add carefully 0.6 mL of ninhydrin TS, shake, and allow to stand at 25°C: the solution shows a red color first, then changes to purple color within 100 minutes.

(4) Pour and spread out 2 to 3 mL of the viscous fluid obtained in (2) onto a glass plate, and allow the water to evaporate: a transparent film results.

(5) Pipet 50 mL of water, add exactly 50 mL of the viscous fluid obtained in (2), and warm to raise the temperature at a rate of 2 to 5°C per minute while stirring: the temperature, when a white turbidity of the solution starts to increase, is not less than 50°C.

Viscosity ⟨*2.53*⟩ (i) Method I: Apply to Hypromellose having a labeled viscosity of less than 600 mPa·s. Put an exact amount of Hypromellose, equivalent to 4.000 g calculated on the dried basis, in a tared, wide-mouth bottle, add water (between 90°C and 99°C) to make 200 g, stopper the bottle, stir by mechanical means at 350 to 450 revolutions per minute for 10 to 20 minutes to get a homogeneous dispersion. If necessary, take off the sample attached on the walls of the bottle, put them in the dispersed solution, and dissolve by continuing the stirring in a water bath at not exceeding 10°C for 20 to 40 minutes. Add cold water, if necessary, to make 200 g, and use this solution as the sample solution. Centrifuge the solution if necessary to expel any entrapped air bubbles. Perform the test with the sample solution at 20 ± 0.1°C as directed in Method I under Viscosity Determination: not less than 80% and not more than 120% of the labeled viscosity.

(ii) Method II: Apply to Hypromellose having a labeled

viscosity of not less than 600 mPa·s. Put an exact amount of Hypromellose, equivalent to 10.00 g calculated on the dried basis, in a tared, wide-mouth bottle, add water (between 90°C and 99°C) to make 500 g, and prepare the sample solution in the same manner as directed in Method I. Perform the test with the sample solution at 20 ± 0.1°C as directed in Method II under Viscosity Determination, using a single cylinder-type rotational viscometer, according to the following operating conditions: not less than 75% and not more than 140% of the labeled viscosity.

Operating conditions—

Apparatus: Brookfield type viscometer LV model or an equivalent apparatus.

Rotor No., rotation frequency, and calculation multiplier: According to the following table, depending on the labeled viscosity.

Labeled viscosity (mPa·s)				Rotor No.	Rotation frequency /min	Calculation multiplier
Not less than 600 and less than			1400	3	60	20
〃	1400	〃	3500	3	12	100
〃	3500	〃	9500	4	60	100
〃	9500	〃	99,500	4	6	1000
〃	99,500			4	3	2000

Procedure of apparatus: Read the value after 2 minutes of rotation, and stop the rotation for at least 2 minutes. Repeat this procedure more two times, and average the three observed values.

pH ⟨*2.54*⟩ The pH of the sample solution obtained in the Viscosity, measured after 5 minutes immersing the electrode in the sample solution, is between 5.0 and 8.0.

◇**Purity** Heavy metals—Put 1.0 g of Hypromellose in a 100-mL Kjeldahl flask, add a sufficient amount of a mixture of nitric acid and sulfuric acid (5:4) to wet the sample, and heat gently. Repeat this procedure until to use totally 18 mL of the mixture of nitric acid and sulfuric acid (5:4). Then boil gently until the solution changes to black. After cooling, add 2 mL of nitric acid, and heat until the solution changes to black. Repeat this procedure until the solution no longer changes to black, and heat strongly until dense white fumes are evolved. After cooling, add 5 mL of water, boil gently until dense white fumes are evolved, then heat until the volume of the solution becomes to 2 to 3 mL. After cooling, if the solution reveals yellow color by addition of 5 mL of water, add 1 mL of hydrogen peroxide (30), and heat until the volume of the solution becomes to 2 to 3 mL. After cooling, dilute the solution with 2 to 3 mL of water, transfer to a Nessler tube, add water to make 25 mL, and use this solution as the sample solution. Separately, put 2.0 mL of Standard Lead Solution in a 100-mL Kjeldahl flask, add 18 mL of the mixture of nitric acid and sulfuric acid (5:4) and an amount of nitric acid equal to that used for preparation of the sample solution, and heat until white fumes are evolved. After cooling, add 10 mL of water. In the case where hydrogen peroxide (30) is added for the preparation of the sample solution, add the same amount of hydrogen peroxide (30), then proceed in the same manner for preparation of the sample solution, and use so obtained solution as the control solution. Adjust the sample solution and the control solution to pH 3.0 to 4.0 with ammonia solution (28), and add water to make 40 mL, respectively. To these solutions add 1.2 mL of thioacetamide-alkaline glycerin TS, 2 mL of acetate buffer solution (pH 3.5) and water to make 50 mL, separately. After allowing to stand for 5 minutes, observe vertically both tubes on a white background: the color obtained with the sample solution is not more intense than that with the control solution (not more than 20 ppm).◇

Loss on drying ⟨*2.41*⟩ Not more than 5.0% (1 g, 105°C, 1 hour).

Residue on ignition ⟨*2.44*⟩ Not more than 1.5% (1 g).

Assay (i) Apparatus—Reaction vial: A 5-mL pressure-tight serum vial, having 20 mm in outside diameter and 50 mm in height, the neck 20 mm in outside diameter and 13 mm in inside diameter, equipped with a septum of butyl-rubber processed the surface with fluoroplastics, which can be fixed tightly to vial with aluminum cap, or equivalent.

Heater: A square-shaped aluminum block, having holes 20 mm in diameter and 32 mm in depth, adopted to the reaction vial. Capable of stirring the content of the reaction vial by means of magnetic stirrer or of reciprocal shaker about 100 times per minute.

(ii) Procedure—Weigh accurately about 65 mg of Hypromellose, transfer to the reaction vial, add 60 to 100 mg of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid, immediately stopper the vial tightly, and weigh accurately. Using a magnetic stirrer equipped in the heating module, or using a shaker, stir for 60 minutes while heating so that the temperature of the vial content is 130 ± 2°C. In the case when a magnetic stirrer or shaker is not available, heat for 30 minutes with repeated shaking at 5-minute intervals by hand, and continue heating for an additional 30 minutes. Allow the vial to cool, and again weigh accurately. If the mass loss is not more than 26 mg and there is no evidence of a leak of the content, use the upper layer of the mixture as the sample solution. Separately, put 60 to 100 mg of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid in a reaction vial, immediately stopper the vial tightly, and weigh accurately. Add 45 μL of iodomethane for assay and 15 to 22 μL of isopropyl iodide for assay through the septum using a micro-syringe with weighing accurately every time, shake thoroughly, and use the upper layer of the content as the standard solution. Perform the test with 1 to 2 μL each of the sample solution and standard solution as directed under Gas Chromatography ⟨*2.02*⟩ according to the following conditions, and calculate the ratios, Q_{Ta} and Q_{Tb}, of the peak area of iodomethane and isopropyl iodide to that of the internal standard obtained from the sample solution, and Q_{Sa} and Q_{Sb}, of the peak area of iodomethane and isopropyl iodide to that of the internal standard from the

standard solution.

$$\text{Content (\%) of methoxy group } (CH_3O) = M_{Sa}/M \times Q_{Ta}/Q_{Sa} \times 21.86$$

$$\text{Content (\%) of hydroxypropoxy group } (C_3H_7O_2) = M_{Sb}/M \times Q_{Tb}/Q_{Sb} \times 44.17$$

M_{Sa}: Amount (mg) of iodomethane for assay taken
M_{Sb}: Amount (mg) of isopropyl iodide for assay taken
M: Amount (mg) of Hypromellose taken, calculated on the dried basis

Internal standard solution—A solution of *n*-octane in *o*-xylene (3 in 100).

Operating conditions—

Detector: A thermal conductivity detector or hydrogen flame-ionization detector.

Column: A fused silica column 0.53 mm in inside diameter and 30 m in length, coated with dimethylpolysiloxane for gas chromatography in 3 μm thickness. Use a guard column, if necessary.

Column temperature: Maintain the temperature at 50°C for 3 minutes, raise to 100°C at a rate of 10°C per minute, then raise to 250°C at a rate of 35°C per minute, and maintain at 250°C for 8 minutes.

Injection port temperature: A constant temperature of about 250°C.

Detector temperature: A constant temperature of about 280°C.

Carrier gas: Helium.

Flow rate: 4.3 mL per minute (the retention time of the internal standard is about 10 minutes).

Split ratio: 1:40.

System suitability—

System performance: When the procedure is run with 1 – 2 μL of the standard solution under the above operating conditions, iodomethane, isopropyl iodide and the internal standard are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 1 – 2 μL of the standard solution under the above operating conditions, the relative standard deviations of the ratio of the peak area of iodomethane and isopropyl iodide to that of the internal standard are not more than 2.0%, respectively.

◆**Containers and storage** Containers—Well-closed containers.◆

Imipramine Hydrochloride

イミプラミン塩酸塩

Change the Melting point as follows:

Melting point ⟨*2.60*⟩ 172 – 176°C (with decomposition).

Imipramine Hydrochloride Tablets

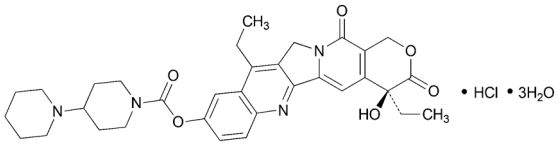
イミプラミン塩酸塩錠

Delete the Identification (3):

Add the following:

Irinotecan Hydrochloride Hydrate

イリノテカン塩酸塩水和物



$C_{33}H_{38}N_4O_6.HCl.3H_2O$: 677.18

(4*S*)-4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl [1,4′-bipiperidine]-1′-carboxylate monohydrochloride trihydrate [*136572-09-3*]

Irinotecan Hydrochloride Hydrate contains not less than 99.0% and not more than 102.0% of irinotecan hydrochloride ($C_{33}H_{38}N_4O_6.HCl$: 623.14), calculated on the anhydrous basis.

Description Irinotecan Hydrochloride Hydrate occurs as pale yellow to light yellow, crystals or crystalline powder.

It is sparingly soluble in methanol, and slightly soluble in water and in ethanol (99.5).

It is gradually colored to yellow-brown and decomposed by light.

Melting point: about 255°C (with decomposition).

It shows crystal polymorphism.

Identification **(1)** Determine the absorption spectrum of a solution of Irinotecan Hydrochloride Hydrate in methanol (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Irinotecan Hydrochloride Hydrate as directed in the potassium bromide disk method under Infrared Spectrophotometry ⟨*2.25*⟩, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) To 1 g of Irinotecan Hydrochloride Hydrate add 50 mL of water, dissolve by heating, and cool: the solution responds to Qualitative Tests ⟨*1.09*⟩ (2) for chloride.

Optical rotation ⟨*2.49*⟩ $[\alpha]_D^{20}$: + 64 – + 69° (0.5 g calculated on the anhydrous basis, water, heat, after cooling, 50 mL, 100 mm).

pH ⟨*2.54*⟩ Dissolve 1 g of Irinotecan Hydrochloride Hy-

drate in 50 mL of water by heating, and cool: the pH of this solution is between 3.5 and 4.5.

Purity **(1)** Heavy metals <*1.07*>—Proceed with 2.0 g of Irinotecan Hydrochloride Hydrate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Related substances—Dissolve 50 mg of Irinotecan Hydrochloride Hydrate in a suitable amount of a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and acetonitrile (6:4:3) and 1 mL of 1 mol/L hydrochloric acid TS, and add a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and acetonitrile (6:4:3) to make 20 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and acetonitrile (6:4:3) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the peak areas of related substances A and B, having the relative retention time of about 0.8 to irinotecan, and related substances C and D, having the relative retention time of about 1.6, obtained from the sample solution are not larger than 1/5 times the peak area of irinotecan from the standard solution, and the area of the peak other than irinotecan and the peaks mentioned above from the sample solution is not larger than 1/10 times the peak area of irinotecan from the standard solution. Furthermore, the total area of the peaks other than irinotecan from the sample solution is not larger than 4/5 times the peak area of irinotecan from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: Dissolve 1.22 g of sodium 1-decanesulfonate in a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and acetonitrile (6:4:3) to make 1000 mL.

Flow rate: Adjust so that the retention time of irinotecan is about 12 minutes.

Time span of measurement: About 3 times as long as the retention time of irinotecan.

System suitability—

Test for required detectability: Pipet 1 mL of the standard solution, and add a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and acetonitrile (6:4:3) to make exactly 20 mL. Confirm that the peak area of irinotecan obtained with 20 μL of this solution is equivalent to 3.5 to 6.5% of that with 20 μL of the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of irinotecan are not less than 6000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of irinotecan is not more than 2.0%.

(3) Enantiomer—Being specified separately when the drug is granted approval based on the Law.

Water <*2.48*> 7.5 – 9.5% (0.1 g, volumetric titration, direct titration).

Residue on ignition <*2.44*> Not more than 0.1% (1 g).

Assay Weigh accurately about 0.44 g of Irinotecan Hydrochloride Hydrate, dissolve in 120 mL of a mixture of acetic anhydride and acetic acid (100) (7:3), and titrate <*2.50*> with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination in the same manner, and make any necessary correction.

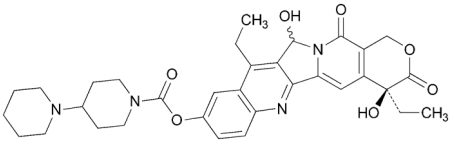
Each mL of 0.1 mol/L perchloric acid VS
= 31.16 mg of $C_{33}H_{38}N_4O_6.HCl$

Containers and storage Containers—Tight containers.

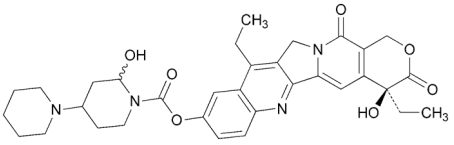
Storage—Light-resistant.

Others

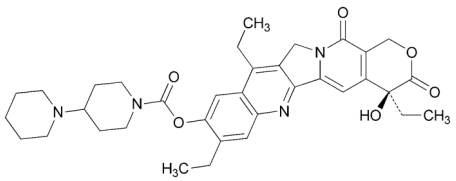
Related substance A:
(4*S*)-4,11-Diethyl-4,12-dihydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl [1,4′-bipiperidine]-1′-carboxylate



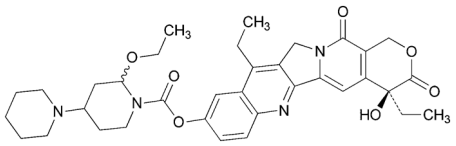
Related substance B:
(4*S*)-4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 2′-hydroxy-[1,4′-bipiperidine]-1′-carboxylate



Related substance C:
(4*S*)-4,8,11-Triethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl [1,4′-bipiperidine]-1′-carboxylate



Related substance D:
(4*S*)-4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 2′-ethoxy-[1,4′-bipiperidine]-1′-carboxylate

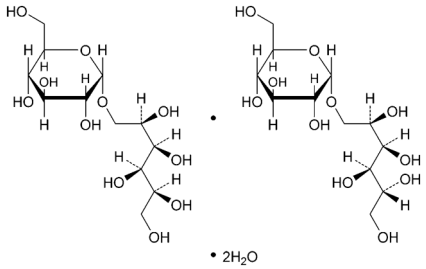


Isomalt Hydrate

Isomalt

イソマル水和物

Change as follows:



6-*O*-α-D-Glucopyranosyl-D-glucitol $C_{12}H_{24}O_{11}$: 344.31
1-*O*-α-D-Glucopyranosyl-D-mannitol dihydrate
$C_{12}H_{24}O_{11}.2H_2O$: 380.34
6-*O*-α-D-Glucopyranosyl-D-glucitol—1-*O*-α-D-glucopyranosyl-D-mannitol dihydrate
[*64519-82-0*]

This monograph is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Isomalt Hydrate is a mixture of 6-*O*-α-D-glucopyranosyl-D-sorbitol and 1-*O*-α-D-glucopyranosyl-D-mannitol.

It contains not less than 98.0% and not more than 102.0% as the mixture of 6-*O*-α-D-glucopyranosyl-D-sorbitol ($C_{12}H_{24}O_{11}$) and 1-*O*-α-D-glucopyranosyl-D-mannitol ($C_{12}H_{24}O_{11}$), calculated on the anhydrous basis, and the amount of each component is not less than 3.0%, respectively.

The label states the contents (%) of 6-*O*-α-D-glucopyranosyl-D-sorbitol and 1-*O*-α-D-glucopyranosyl-D-mannitol.

◆**Description** Isomalt Hydrate occurs as a white, powder or grains.

It is freely soluble in water, and practically insoluble in ethanol (95).

Optical rotation $[\alpha]_D^{20}$: about + 92° (1 g calculated on the anhydrous basis, water, 100 mL, 100 mm).◆

Identification ◇**(1)** To 1 mL of a solution of Isomalt Hydrate (1 in 100) add 1 mL of a solution of catechol (1 in 10) prepared before use, shake thoroughly, add 2 mL of sulfuric acid rapidly, and shake: a reddish purple to red-purple color develops.◇

(2) Perform the test with 20 μL each of the sample solution and standard solution obtained in the Assay as directed under Liquid Chromatography <*2.01*> according to the following conditions, and compare the chromatograms obtained from these solutions: the two principal peaks in the chromatogram obtained from the sample solution are similar in retention time to respective two peaks from the standard solution.

Operating conditions—

Proceed as directed in the operating conditions in the Assay.

System suitability—

Proceed as directed in the system suitability in the Assay.

Purity ◇**(1)** Heavy metals <*1.07*>—Proceed with 2.0 g of Isomalt Hydrate according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).◇

(2) Nickel—Weigh exactly an amount of Isomalt Hydrate, equivalent to 10.0 g calculated on the anhydrous basis, dissolve in 30 mL of 2 mol/L acetic acid TS, and add water to make exactly 100 mL. Add exactly 2 mL of a solution of ammonium pyrrolidinedithiocarbamate (1 in100) and exactly 10 mL of water-saturated 4-methyl-2-pentanone, and shake for 30 seconds protected from light. Allow the layers to separate, and use the 4-methyl-2-pentanone layer as the sample solution. Separately, take in three vessels three exact portions of Isomalt Hydrate, each equivalent to 10.0 g calculated on the anhydrous basis, dissolve in 30 mL of 2 mol/L acetic acid TS, then add exactly 0.5 mL, 1.0 mL and 1.5 mL respectively of Standard Nickel Solution for Atomic Absorption Spectrophotometry, and add water to make them exactly 100 mL. Then, proceed in the same manner as the sample solution, and use the solutions so obtained as the standard solutions. Separately, prepare 4-methyl-2-pentanone layer by proceeding in the same manner as the sample solution but omitting the substance to be examined, and use this solution as the blank solution. Perform the test with the sample solution and standard solution as directed in the standard addition method under Atomic Absorption Spectrophotometry <*2.23*> according to the following conditions. The blank solution is used to set the zero of

the instrument, and to ascertain that the readings return to zero after rinsing the sample introduction system with water between each measurement: the amount of nickel is not more than 1 ppm.

Gas: Combustible gas—Acetylene.
Supporting gas—Air.
Lamp: Nickel hollow-cathode lamp.
Wavelength: 232.0 nm.

(3) Related substances—Weigh exactly 0.20 g of Isomalt Hydrate, dissolve in water to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh exactly 10.0 mg of D-sorbitol and 10.0 mg of D-mannitol, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine each peak area by the automatic integration method: the peak areas of D-mannitol, having a relative retention time of about 1.6 to 1-*O*-α-D-glucopyranosyl-D-mannitol, and D-sorbitol, having a relative retention time of about 2.0, obtained from the sample solution are not larger than the area of the corresponding peak from the standard solution (not more than 0.5%), and the area of the peak other of 1-*O*-α-D-glucopyranosyl-D-mannitol and 6-*O*-α-D-glucopyranosyl-D-sorbitol having a relative retention time of about 1.2 and the peaks mentioned above from the sample solution is not larger than the peak area of D-sorbitol from the standard solution (not more than 0.5%). In addition, the total area of the peaks other than 1-*O*-α-D-glucopyranosyl-D-mannitol and 6-*O*-α-D-glucopyranosyl-D-sorbitol from the sample solution is not larger than 4 times the peak area of D-sorbitol from the standard solution (not more than 2.0%). However, the peaks which area is not larger than 1/5 times the peak area of D-sorbitol from the standard solution are disregarded (not more than 0.1%).

Operating conditions—

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 2.5 times as long as the retention time of 1-*O*-α-D-glucopyranosyl-D-mannitol.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

◇Test for required detectability: Pipet 2 mL of the standard solution, and add water to make exactly 10 mL. Confirm that the peak area of D-sorbitol obtained with 20 μL of this solution is equivalent to 14 to 26% of that with 20 μL the standard solution.◇

◇System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviations of the peak area of D-mannitol and D-sorbitol are not more than 2.0%, respectively.◇

(4) Reducing sugars—Dissolve 3.3 g of Isomalt Hydrate in 10 mL of water with the aid of gentle heat, cool, and add 20 mL of copper (II) citrate TS. Add a few amount of boiling chips, heat so that the boiling begins after 4 minutes, and maintain boiling for 3 minutes. Cool rapidly, add 100 mL of a solution of acetic acid (100) (3 in 125) and exactly 20 mL of 0.025 mol/L iodine VS. With continuous shaking, add 25 mL of a mixture of water and hydrochloric acid (47:3). When the precipitate has dissolved, titrate <*2.50*> the excess of iodine with 0.05 mol/L sodium thiosulfate VS, until the blue color due to 1 mL of soluble starch TS added at near of the end point disappears: not less than 12.8 mL of 0.05 mol/L sodium thiosulfate VS is required (not more than 0.3% as glucose).

Conductivity <*2.51*> Dissolve 20 g of Isomalt Hydrate in a suitable amount of freshly boiled and cooled water with the aid of gentle heat at 40 – 50°C, cool, add the same water to make exactly 100 mL, and use this solution as the sample solution. Measure the conductivity (25°C) of the sample solution at 25 ± 0.1°C while gently stirring with a magnetic stirrer: not more than 20 $\mu S \cdot cm^{-1}$.

Water <*2.48*> Not more than 7.0% (0.3 g, volumetric titration, direct titration. Use a mixture of methanol for water determination and formamide for water determination (1:1) heated at 50 ± 5°C instead of methanol for water determination).

Assay Weight accurately about 0.2 g of Isomalt Hydrate, dissolve in water to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.2 g of Isomalt RS (separately determine the water <*2.48*> in the same manner as Isomalt Hydrate), dissolve in water to make exactly 10 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_{Ta} and A_{Tb}, and A_{Sa} and A_{Sb}, of 1-*O*-α-D-glucopyranosyl-D-mannitol and 6-*O*-α-D-glucopyranosyl-D-sorbitol in each solution.

Amount (g) of 1-*O*-α-D-glucopyranosyl-D-mannitol ($C_{12}H_{24}O_{11}$)
$= M_S \times K_a/100 \times A_{Ta}/A_{Sa}$

Amount (g) of 6-*O*-α-D-glucopyranosyl-D-sorbitol ($C_{12}H_{24}O_{11}$)
$= M_S \times K_b/100 \times A_{Tb}/A_{Sb}$

M_S: Amount (g) of Isomalt RS taken, calculated on the anhydrous basis
K_a: Content (%) of 1-*O*-α-D-glucopyranosyl-D-mannitol ($C_{12}H_{24}O_{11}$) in Isomalt RS
K_b: Content (%) of 6-*O*-α-D-glucopyranosyl-D-sorbitol ($C_{12}H_{24}O_{11}$) in Isomalt RS

Operating conditions—

Detector: A differential refractometer maintained at a constant temperature (40°C for example).

Column: Two stainless steel columns, 4.6 mm in inside diameter and 3 cm in length, and 7.8 mm in inside diameter and 30 cm in length, both packed with strongly acidic ion-

exchange resin (Ca type) for liquid chromatography with sulfonic acid groups attached to a polymer lattice consisting of polystyrene cross-linked with divinylbenzene (degree of cross-linkage: 8%) (9 μm in particle diameter). These are used as the pre-column and the separation column, respectively.

Column temperature: 80 ± 3°C.

Mobile phase: Water.

Flow rate: 0.5 mL per minute (retention time of 1-*O*-α-D-glucopyranosyl-D-mannitol is about 12 minutes).

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, 1-*O*-α-D-glucopyranosyl-D-mannitol and 6-*O*-α-D-glucopyranosyl-D-sorbitol are eluted in this order with the resolution between these peaks being not less than 2.0.

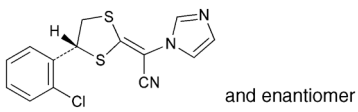
◇System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of 1-*O*-α-D-glucopyranosyl-D-mannitol and 6-*O*-α-D-glucopyranosyl-D-sorbitol is not more than 2.0%, respectively.◇

◆**Containers and storage** Containers—Well-closed containers.◆

Add the following:

Lanoconazole

ラノコナゾール



and enantiomer

$C_{14}H_{10}ClN_3S_2$: 319.83

(2*E*)-2-[(4*RS*)-4-(2-Chlorophenyl)-1,3-dithiolan-2-ylidene]-2-(1*H*-imidazol-1-yl)acetonitrile

[*101530-10-3*]

Lanoconazole, when dried, contains not less than 98.0% and not more than 102.0% of lanoconazole ($C_{14}H_{10}ClN_3S_2$).

Description Lanoconazole occurs as white to pale yellow, crystals or crystalline powder.

It is soluble in acetone, sparingly soluble in methanol and in ethanol (99.5), and practically insoluble in water.

It is gradually colored to yellow by light.

A solution of Lanoconazole in acetone (1 in 25) shows no optical rotation.

Identification (1) To 0.1 g of Lanoconazole add 0.5 g of sodium hydroxide, heat gradually to melt, and carbonize. After cooling, add 10 mL of dilute hydrochloric acid: the gas evolved darkens moistened lead (II) acetate paper.

(2) Perform the test with Lanoconazole as directed under Flame Coloration Test <*1.04*> (2): a green color appears.

(3) Determine the absorption spectrum of a solution of Lanoconazole in methanol (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Lanoconazole RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared absorption spectrum of Lanoconazole, previously dried, as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum or the spectrum of previously dried Lanoconazole RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Melting point <*2.60*> 141 – 146°C

Purity (1) Heavy metals <*1.07*>—Proceed with 2.0 g of Lanoconazole according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Related substances—Conduct this procedure using light-resistant vessels. Dissolve 0.10 g of Lanoconazole in 100 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the total area of the peaks other than lanoconazole obtained from the sample solution is not larger than 1/2 times the peak area of lanoconazole from the standard solution.

Operating conditions—

Detector, column, and column temperature: Proceed as directed in the operating conditions in the Assay.

Mobile phase: Dissolve 0.576 g of sodium 1-nonanesulfonate in 1000 mL of a mixture of methanol, water and acetic acid (100) (55:44:1).

Flow rate: Adjust so that the retention time of lanoconazole is about 7 minutes.

Time span of measurement: About 3 times as long as the retention time of lanoconazole, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 2.5 mL of the standard solution, and add methanol to make exactly 50 mL. Confirm that the peak area of lanoconazole obtained with 5 μL of this solution is equivalent to 3.5 to 6.5% of that with 5 μL of the standard solution.

System performance: Put 20 mL of the sample solution in a colorless vessel, and expose to ultraviolet light (main wavelength: 365 nm) for 30 minutes. When the procedure is run with 5 μL of this solution under the above operating conditions, the resolution between the peak having the relative retention time of about 0.8 to lanoconazole and the

peak of lanoconazole is not less than 1.5.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of lanoconazole is not more than 1.0%.

Loss on drying ⟨*2.41*⟩ Not more than 0.4% (1 g, 105°C, 2 hours).

Residue on ignition ⟨*2.44*⟩ Not more than 0.1% (1 g).

Assay Conduct this procedure using light-resistant vessels. Weigh accurately about 50 mg each of Lanoconazole and Lanoconazole RS, both previously dried, and dissolve each in methanol to make exactly 50 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal standard solution, add methanol to make 50 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of lanoconazole to that of the internal standard.

$$\text{Amount (mg) of lanoconazole } (C_{14}H_{10}ClN_3S_2) = M_S \times Q_T/Q_S$$

M_S: Amount (mg) of Lanoconazole RS taken

Internal standard solution—A solution of diisopropyl 1,3-dithiolan-2-ylidenemalonate in methanol (1 in 1000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 295 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 50°C.

Mobile phase: A mixture of methanol and water (11:9).

Flow rate: Adjust so that the retention time of lanoconazole is about 9 minutes.

System suitability—

System performance: When the procedure is run with 5 μL of the standard solution under the above operating conditions, lanoconazole and the internal standard are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of lanoconazole to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Well-closed containers.

Storage—Light-resistant.

Add the following:

Lanoconazole Cream

ラノコナゾールクリーム

Lanoconazole Cream contains not less than 95.0% and not more than 105.0% of the labeled amount of lanoconazole ($C_{14}H_{10}ClN_3S_2$: 319.83).

Method of preparation Prepare as directed under Creams, with Lanoconazole.

Identification Warm Lanoconazole Cream to soften, if necessary. To a quantity of Lanoconazole Cream, equivalent to 50 mg of Lanoconazole, add 10 mL of diluted hydrochloric acid (1 in 6) saturated with sodium chloride, previously warmed, shake vigorously for 15 minutes to disperse, and centrifuge. Filter the supernatant liquid, wash the residue with 1.5 mL of diluted hydrochloric acid (1 in 6) saturated with sodium chloride, filter, and combine the washing with the filtrate. To the combined filtrate add 2.5 g of sodium hydrogen carbonate to dissolve, and extract with 10 mL of diethyl ether. Wash the diethyl ether layer with three 10-mL portions of water, and dry under reduced pressure. Dissolve the residue in 15 mL of acetone, and use this solution as the sample solution. Separately, dissolve 10 mg of lanoconazole in 10 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography ⟨*2.03*⟩. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, toluene, methanol and ammonia solution (28) (400:400:20:1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the principal spot obtained from the sample solution and the spot from the standard solution show the same *R*f value.

Assay Conduct this procedure using light-resistant vessels. Weigh accurately a quantity of Lanoconazole Cream, equivalent to about 15 mg of lanoconazole ($C_{14}H_{10}ClN_3S_2$), add 80 mL of methanol, sonicate to disperse, and add exactly 10 mL of the internal standard solution. Add methanol to make 100 mL, filter through a membrane filter with a pore size of 0.45 μm if necessary, and use this solution as the sample solution. Separately, weigh accurately about 15 mg of Lanoconazole RS, previously dried at 105°C for 2 hours, dissolve in methanol, and add exactly 10 mL of the internal standard solution. Add methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of lanoconazole to that of the internal standard.

$$\text{Amount (mg) of lanoconazole } (C_{14}H_{10}ClN_3S_2) = M_S \times Q_T/Q_S$$

M_S: Amount (mg) of Lanoconazole RS taken

Internal standard solution—A solution of diisopropyl 1,3-dithiolan-2-ylidenemalonate in methanol (1 in 1000).

Operating conditions—

Proceed as directed in the operating conditions in the Assay under Lanoconazole.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, lanoconazole and the internal standard are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of lanoconazole to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Add the following:

Lanoconazole Cutaneous Solution

ラノコナゾール外用液

Lanoconazole Cutaneous Solution is a liquid for external use.

It contains not less than 95.0% and not more than 105.0% of the labeled amount of lanoconazole ($C_{14}H_{10}ClN_3S_2$: 319.83).

Method of preparation Prepare as directed under Liquids and Solutions for Cutaneous Application, with Lanoconazole.

Identification To a volume of Lanoconazole Cutaneous Solution, equivalent to 50 mg of Lanoconazole, add water enough to produce precipitate, and shake vigorously. Filter this solution, rinse the vessel with a suitable amount of water, and collect the precipitates. Wash the precipitates with 100 mL of water, dissolve in acetone, and dry under reduced pressure. If there are water droplets in the residue, dissolve the residue in 40 mL of acetone, and dry again under reduced pressure. Dissolve the residue in 30 mL of acetone, and use this solution as the sample solution. Separately, dissolve 10 mg of lanoconazole in 10 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, toluene, methanol and ammonia solution (28) (400:400:20:1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the principal spot obtained from the sample solution and the spot from the standard solution show the same *R*f value.

Assay Conduct this procedure using light-resistant vessels. Pipet a volume of Lanoconazole Cutaneous Solution, equivalent to about 50 mg of lanoconazole ($C_{14}H_{10}ClN_3S_2$), and add methanol to make exactly 50 mL. Pipet 15 mL of this solution, add exactly 10 mL of the internal standard solution, add methanol to make 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 15 mg of Lanoconazole RS, previously dried at 105°C for 2 hours, dissolve in methanol, and add exactly 10 mL of the internal standard solution. Add methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of lanoconazole to that of the internal standard.

$$\text{Amount (mg) of lanoconazole } (C_{14}H_{10}ClN_3S_2) = M_S \times Q_T/Q_S \times 10/3$$

M_S: Amount (mg) of Lanoconazole RS taken

Internal standard solution—A solution of diisopropyl 1,3-dithiolan-2-ylidenemalonate in methanol (1 in 1000).

Operating conditions—

Proceed as directed in the operating conditions in the Assay under Lanoconazole.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, lanoconazole and the internal standard are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of lanoconazole to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Add the following:

Lanoconazole Ointment

ラノコナゾール軟膏

Lanoconazole Ointment contains not less than 93.0% and not more than 107.0% of the labeled amount of lanoconazole ($C_{14}H_{10}ClN_3S_2$: 319.83).

Method of preparation Prepare as directed under Ointments, with Lanoconazole.

Identification To a quantity of Lanoconazole Ointment, equivalent to 50 mg of Lanoconazole, add 15 mL of hexane, sonicate to disperse, add 10 mL of methanol, and shake for 10 minutes. Centrifuge this solution, discard the hexane

layer, and take the methanol layer. Wash the residue with a small amount of methanol if necessary, and combine the washing with the methanol layer. Dry the combined methanol layer under reduced pressure, dissolve the residue in 40 mL of acetone, and use this solution as the sample solution. Separately, dissolve 10 mg of lanoconazole in 10 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, toluene, methanol and ammonia solution (28) (400:400:20:1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the principal spot obtained from the sample solution and the spot from the standard solution show the same *R*f value.

Assay Conduct this procedure using light-resistant vessels. Weigh accurately a quantity of Lanoconazole Ointment, equivalent to about 15 mg of lanoconazole ($C_{14}H_{10}ClN_3S_2$), add 20 mL of tetrahydrofuran, sonicate to disperse, and add exactly 10 mL of the internal standard solution. Add methanol to make 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 15 mg of Lanoconazole RS, previously dried at 105°C for 2 hours, dissolve in methanol, and add exactly 10 mL of the internal standard solution. Add methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of lanoconazole to that of the internal standard.

$$\text{Amount (mg) of lanoconazole } (C_{14}H_{10}ClN_3S_2) = M_S \times Q_T/Q_S$$

M_S: Amount (mg) of Lanoconazole RS taken

Internal standard solution—A solution of diisopropyl 1,3-dithiolan-2-ylidenemalonate in methanol (1 in 1000).

Operating conditions—

Proceed as directed in the operating conditions in the Assay under Lanoconazole.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, lanoconazole and the internal standard are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of lanoconazole to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Mestranol

メストラノール

Change the Description and Optical rotation as follows:

Description Mestranol occurs as a white to pale yellow-white crystalline powder. It is odorless.

It is freely soluble in chloroform, sparingly soluble in ethanol (99.5), and practically insoluble in water.

Optical rotation <*2.49*> $[\alpha]_D^{25}$: +1 – +6° (after drying, 0.1 g, ethanol (99.5), 10 mL, 100 mm).

Change the following as follows:

Methylcellulose

メチルセルロース

[*9004-67-5*]

This monograph is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia.

The corresponding part of the attributes/provisions which are agreed as non-harmonized within the scope of the harmonization is marked with symbols (◆ ◆), and the corresponding parts which are agreed as the JP local requirement other than the scope of the harmonization are marked with symbols (◇ ◇).

Methylcellulose is a methyl ether of cellulose.

It contains not less than 26.0% and not more than 33.0% of methoxy group (-OCH_3: 31.03), calculated on the dried basis.

The viscosity of Methylcellulose is shown in millipascal second (mPa·s).

◆**Description** Methylcellulose occurs as a white to yellowish white, powder or grains.

It is practically insoluble in ethanol (99.5).

It swells, when water is added, and forms a clear or slightly turbid, viscous liquid.◆

Identification **(1)** Disperse evenly 1.0 g of Methylcellulose over the surface of 100 mL of water in a beaker, while gently tapping the top of the beaker, if necessary, and allow the beaker to stand: it aggregates on the surface of water.

(2) Add 1.0 g of Methylcellulose to 100 mL of hot water, and stir: it becomes a suspension. Cool the suspension to 5°C, and stir: the resulting liquid is a clear or a slightly cloudy, viscous fluid.

(3) To 0.1 mL of the viscous fluid obtained in (2) add 9 mL of diluted sulfuric acid (9 in 10), shake, heat in a water bath for exactly 3 minutes, and immediately cool in ice water. Add carefully 0.6 mL of ninhydrin TS, shake, and allow to stand at 25°C: the solution shows a red color, and

it does not change to purple color within 100 minutes.

(4) Pour and spread out 2 to 3 mL of the viscous fluid obtained in (2) onto a glass plate, and allow the water to evaporate: a transparent film results.

(5) Pipet 50 mL of water, add exactly 50 mL of the viscous fluid obtained in (2), and warm to raise the temperature at a rate of 2 to 5°C per minute while stirring: the temperature, when a white turbidity of the solution starts to increase, is not less than 50°C.

Viscosity ⟨*2.53*⟩ (i) Method I: Apply to Methylcellulose having a labeled viscosity of less than 600 mPa·s. Put an exact amount of Methylcellulose, equivalent to 4.000 g, calculated on the dried basis, in a tared, wide-mouth bottle, add water (between 90°C and 99°C) to make 200 g, stopper the bottle, stir by mechanical means at 350 to 450 revolutions per minute for 10 to 20 minutes to get a homogeneous dispersion. If necessary, take off the sample attached on the walls of the bottle, put them in the dispersed solution, and dissolve by continuing the stirring in a water bath at not exceeding 5°C for 20 to 40 minutes. Add cold water, if necessary, to make 200 g, and use this solution as the sample solution. Centrifuge the solution if necessary to expel any entrapped air bubbles. Perform the test with the sample solution at 20 ± 0.1°C as directed in Method I under Viscosity Determination: not less than 80% and not more than 120% of the labeled viscosity.

(ii) Method II: Apply to Methylcellulose having a labeled viscosity of not less than 600 mPa·s. Put an exact amount of Methylcellulose, equivalent to 10.00 g, calculated on the dried basis, in a tared, wide-mouth bottle, add water (between 90°C and 99°C) to make 500 g, and prepare the sample solution in the same manner as directed in Method I. Perform the test with the sample solution at 20 ± 0.1°C as directed in Method II under Viscosity Determination, using a single cylinder-type rotational viscometer, according to the following operating conditions: not less than 75% and not more than 140% of the labeled viscosity.

Operating conditions—

Apparatus: Brookfield type viscometer LV model or an equivalent apparatus.

Rotor No., rotation frequency, and calculation multiplier: According to the following table, depending on the labeled viscosity.

Labeled viscosity (mPa·s)				Rotor No.	Rotation frequency /min	Calculation multiplier
Not less than 600 and less than			1400	3	60	20
〃	1400	〃	3500	3	12	100
〃	3500	〃	9500	4	60	100
〃	9500	〃	99,500	4	6	1000
〃	99,500			4	3	2000

Procedure of apparatus: Read the value after 2 minutes of rotation, and stop the rotation for at least 2 minutes. Repeat this procedure more two times, and average the three observed values.

pH ⟨*2.54*⟩ The pH of the sample solution obtained in the Viscosity, measured after 5 minutes immersing the electrode in the sample solution, is between 5.0 and 8.0.

◇**Purity** Heavy metals—Put 1.0 g of Methylcellulose in a 100-mL Kjeldahl flask, add a sufficient amount of a mixture of nitric acid and sulfuric acid (5:4) to wet the sample, and heat gently. Repeat this procedure until to use totally 18 mL of the mixture of nitric acid and sulfuric acid (5:4). Then boil gently until the solution changes to black. After cooling, add 2 mL of nitric acid, and heat until the solution changes to black. Repeat this procedure until the solution no longer changes to black, and heat strongly until dense white fumes are evolved. After cooling, add 5 mL of water, boil gently until dense white fumes are evolved, then heat until the volume of the solution becomes to 2 to 3 mL. After cooling, if the solution reveals yellow color by addition of 5 mL of water, add 1 mL of hydrogen peroxide (30), and heat until the volume of the solution becomes to 2 to 3 mL. After cooling, dilute the solution with 2 to 3 mL of water, transfer to a Nessler tube, add water to make 25 mL, and use this solution as the sample solution. Separately, put 2.0 mL of Standard Lead Solution in a 100-mL Kjeldahl flask, add 18 mL of the mixture of nitric acid and sulfuric acid (5:4) and an amount of nitric acid equal to that used for preparation of the sample solution, and heat until dense white fumes are evolved. After cooling, add 10 mL of water. In the case where hydrogen peroxide (30) is added for the preparation of the sample solution, add the same amount of hydrogen peroxide (30), then proceed in the same manner for preparation of the sample solution, and use so obtained solution as the control solution. Adjust the sample solution and the control solution to pH 3.0 to 4.0 with ammonia solution (28), and add water to make 40 mL, respectively. To these solutions add 1.2 mL of thioacetamide-alkaline glycerin TS, 2 mL of acetate buffer solution (pH 3.5) and water to make 50 mL, separately. After allowing to stand for 5 minutes, observe vertically both tubes on a white background: the color obtained with the sample solution is not more intense than that with the control solution (not more than 20 ppm).◇

Loss on drying ⟨*2.41*⟩ Not more than 5.0% (1 g, 105°C, 1 hour).

Residue on ignition ⟨*2.44*⟩ Not more than 1.5% (1 g).

Assay (i) Apparatus—Reaction vial: A 5-mL pressure-tight serum vial, having 20 mm in outside diameter and 50 mm in height, the neck 20 mm in outside diameter and 13 mm in inside diameter, equipped with a septum of butyl-rubber processed the surface with fluoroplastics, which can be fixed tightly to vial with aluminum cap, or equivalent.

Heater: A square-shaped aluminum block, having holes 20 mm in diameter and 32 mm in depth, adopted to the reaction vial. Capable of stirring the content of the reaction vial by means of magnetic stirrer or of reciprocal shaker about 100 times per minute.

(ii) Procedure—Weigh accurately about 65 mg of Methylcellulose, transfer to the reaction vial, add 60 to 100

mg of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid, immediately stopper the vial tightly, and weigh accurately. Using a magnetic stirrer equipped in the heating module, or using a shaker, stir for 60 minutes while heating so that the temperature of the vial content is 130 ± 2°C. In the case when a magnetic stirrer or shaker is not available, heat for 30 minutes with repeated shaking at 5-minute intervals by hand, and continue heating for an additional 30 minutes. Allow the vial to cool, and again weigh accurately. If the mass loss is not more than 26 mg and there is no evidence of a leak of the content, use the upper layer of the mixture as the sample solution. Separately, put 60 to 100 mg of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid in a reaction vial, immediately stopper the vial tightly, and weigh accurately. Add 45 μL of iodomethane for assay through the septum using a micro-syringe, weigh accurately, shake , and use the upper layer of the mixture as the standard solution. Perform the test with 1 to 2 μL each of the sample solution and standard solution as directed under Gas Chromatography <2.02> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of iodomethane to that of the internal standard.

$$\text{Content (\%) of methoxy group } (CH_3O) = M_S/M \times Q_T/Q_S \times 21.86$$

M_S: Amount (mg) of iodomethane for assay taken
M: Amount (mg) of Methylcellulose taken, calculated on the dried basis

Internal standard solution—A solution of *n*-octane in *o*-xylene (3 in 100).

Operating conditions—

Detector: A thermal conductivity detector or hydrogen flame-ionization detector.

Column: A fused silica column 0.53 mm in inside diameter and 30 m in length, coated with dimethylpolysiloxane for gas chromatography in 3 μm thickness. Use a guard column, if necessary.

Column temperature: Maintain the temperature at 50°C for 3 minutes, raise to 100°C at a rate of 10°C per minute, then raise to 250°C at a rate of 35°C per minute, and maintain at 250°C for 8 minutes.

Injection port temperature: A constant temperature of about 250°C.

Detector temperature: A constant temperature of about 280°C.

Carrier gas: Helium.

Flow rate: 4.3 mL per minute (the retention time of the internal standard is about 10 minutes).

Split ratio: 1:40.

System suitability—

System performance: When the procedure is run with 1 – 2 μL of the standard solution under the above operating conditions, iodomethane and the internal standard are eluted in this order with the resolution between these peaks being not less than 5

System repeatability: When the test is repeated 6 times with 1 – 2 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of iodomethane to that of the internal standard is not more than 2.0%.

◆**Containers and storage** Containers—Well-closed containers.◆

Methylprednisolone

メチルプレドニゾロン

Change the Description and Optical rotation as follows:

Description Methylprednisolone occurs as a white crystalline powder. It is odorless.

It is sparingly soluble in methanol and in ethanol (99.5), and practically insoluble in water.

Melting point: 232 – 240°C (with decomposition).

Optical rotation <2.49> $[\alpha]_D^{25}$: +93 – +103° (after drying, 0.1 g, ethanol (99.5), 10 mL, 100 mm).

Add the following:

Minocycline Hydrochloride Granules

ミノサイクリン塩酸塩顆粒

Minocycline Hydrochloride Granules contain not less than 90.0% and not more than 110.0% of the labeled potency of minocycline ($C_{23}H_{27}N_3O_7$: 457.48).

Method of preparation Prepare as directed under Granules, with Minocycline Hydrochloride.

Identification To a quantity of Minocycline Hydrochloride Granules, equivalent to 10 mg (potency) of Minocycline Hydrochloride, add 625 mL of a solution of hydrochloric acid in methanol (19 in 20,000), shake thoroughly, and filter. Determine the absorption spectrum of the filtrate as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits maxima between 221 nm and 225 nm, between 261 nm and 265 nm, and between 354 nm and 358 nm.

Purity Related substances—Conduct this procedure within 30 minutes after the preparation of the sample solution. To a quantity of Minocycline Hydrochloride Granules, equivalent to 50 mg (potency) of Minocycline Hydrochloride, add 60 mL of the mobile phase, shake vigorously, add the mobile phase to make 100 mL. Centrifuge this solution, and use the supernatant liquid as the sample solution. Perform the test with 20 μL of the sample solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic in-

tegration method, and calculate their amounts by the area percentage method: the amount of the peak of epiminocycline, having the relative retention time of about 0.83 to minocycline, is not more than 4.0%.

Operating conditions—

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay under Minocycline Hydrochloride.

Time span of measurement: About 2.5 times as long as the retention time of minocycline, beginning after the solvent peak.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay under Minocycline Hydrochloride.

Test for required detectability: To 2 mL of the standard solution obtained in the Assay add the mobile phase to make 100 mL, and use this solution as the solution for system suitability test. Pipet 5 mL of the solution for system suitability test, and add the mobile phase to make exactly 100 mL. Confirm that the peak area of minocycline obtained with 20 μL of this solution is equivalent to 3.5 to 6.5% of that with 20 μL of the solution for system suitability test.

System repeatability: When the test is repeated 6 times with 20 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of minocycline is not more than 2.0%.

Water ⟨*2.48*⟩ Not more than 2.0% (4 g of powdered Minocycline Hydrochloride Granules, volumetric titration, back titration).

Uniformity of dosage units ⟨*6.02*⟩ Perform the test according to the following method: Minocycline Hydrochloride Granules in single-dose packages meet the requirement of the Content uniformity test.

To the total content of 1 package of Minocycline Hydrochloride Granules add water to disintegrate, shake thoroughly, add water to make exactly 100 mL, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 20 μg (potency) of minocycline ($C_{23}H_{27}N_3O_7$), and use this solution as the sample solution. Separately, weigh accurately an amount of Minocycline Hydrochloride RS, equivalent to about 20 mg (potency), dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the sample solution and standard solution at 348 nm as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩.

Amount [mg (potency)] of minocycline ($C_{23}H_{27}N_3O_7$)
$= M_S \times A_T/A_S \times V'/V \times 1/10$

M_S: Amount [mg (potency)] of Minocycline Hydrochloride RS taken

Dissolution ⟨*6.10*⟩ When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rate in 15 minutes of Minocycline Hydrochloride Granules is not less than 85%.

Start the test with an accurately weighed amount of Minocycline Hydrochloride Granules, equivalent to about 20 mg (potency) of Minocycline Hydrochloride, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 10 mL of the first filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately an amount of Minocycline Hydrochloride RS, equivalent to about 22 mg (potency), and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the sample solution and standard solution at 348 nm as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩.

Dissolution rate (%) with respect to the labeled amount of minocycline ($C_{23}H_{27}N_3O_7$)
$= M_S/M_T \times A_T/A_S \times 1/C \times 90$

M_S: Amount [mg (potency)] of Minocycline Hydrochloride RS taken

M_T: Amount (g) of Minocycline Hydrochloride Granules taken

C: Labeled amount [mg (potency)] of minocycline ($C_{23}H_{27}N_3O_7$) in 1 g

Assay Weigh accurately an amount of powdered Minocycline Hydrochloride Granules, equivalent to about 50 mg (potency) of Minocycline Hydrochloride, add the mobile phase, shake vigorously, and add the mobile phase to make exactly 100 mL. Centrifuge this solution, and use the supernatant liquid as the sample solution. Separately, weigh accurately an amount of Minocycline Hydrochloride RS, equivalent to about 25 mg (potency), dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay under Minocycline Hydrochloride.

Amount [mg (potency)] of minocycline ($C_{23}H_{27}N_3O_7$)
$= M_S \times A_T/A_S \times 2$

M_S: Amount [mg (potency)] of Minocycline Hydrochloride RS taken

Containers and storage Containers—Tight containers.
Storage—Light-resistant.

Add the following:

Nortriptyline Hydrochloride Tablets

ノルトリプチリン塩酸塩錠

Nortriptyline Hydrochloride Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of nortriptyline ($C_{19}H_{21}N$: 263.38).

Method of preparation Prepare as directed under Tablets, with Nortriptyline Hydrochloride.

Identification **(1)** Determine the absorption spectrum of the sample solution obtained in the Assay as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, using diluted 0.1 mol/L hydrochloric acid TS (1 in 50) as the blank: it exhibits a maximum between 237 nm and 241 nm.

(2) To a quantity of powdered Nortriptyline Hydrochloride Tablets, equivalent to 10 mg of nortriptyline ($C_{19}H_{21}N$), add 10 mL of ethanol (99.5), shake thoroughly, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 11 mg of nortriptyline hydrochloride in 10 mL of ethanol (99.5), and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 1-butanol, water and acetic acid (100) (4:1:1) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the principal spot obtained from the sample solution and the spot from the standard solution show the same *R*f value.

Uniformity of dosage units <*6.02*> Perform the test according to the following method: it meets the requirement of the Content uniformity test.

To 1 tablet of Nortriptyline Hydrochloride Tablets add a suitable volume of 0.1 mol/L hydrochloric acid TS, disperse the fine particles by sonicating, add a suitable volume of 0.1 mol/L hydrochloric acid TS, sonicate, extract for 15 minutes while occasional shaking. Shake for 15 minutes, and add 0.1 mol/L hydrochloric acid TS to make exactly V mL so that each mL contains about 0.5 mg of nortriptyline ($C_{19}H_{21}N$). Centrifuge this solution, pipet 2 mL of the supernatant liquid, add water to make exactly 100 mL, and use this solution as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of nortriptyline ($C_{19}H_{21}N$)
$= M_S \times A_T/A_S \times V/50 \times 0.878$

M_S: Amount (mg) of nortriptyline hydrochloride for assay taken

Dissolution <*6.10*> When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rates in 30 minutes of a 10-mg tablet and a 25-mg tablet are not less than 70% and not less than 80%, respectively.

Start the test with 1 tablet of Nortriptyline Hydrochloride Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 10 mL of the first filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 11 μg of nortriptyline ($C_{19}H_{21}N$), and use this solution as the sample solution. Separately, weigh accurately about 25 mg of nortriptyline hydrochloride for assay, previously dried at 105°C for 2 hours, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the sample solution and standard solution at 239 nm as directed under Ultraviolet-visible Spectrophotometry <*2.24*>.

Dissolution rate (%) with respect to the labeled amount of nortriptyline ($C_{19}H_{21}N$)
$= M_S \times A_T/A_S \times V'/V \times 1/C \times 45 \times 0.878$

M_S: Amount (mg) of nortriptyline hydrochloride for assay taken

C: Labeled amount (mg) of nortriptyline ($C_{19}H_{21}N$) in 1 tablet

Assay Weigh accurately the mass of not less than 20 tablets of Nortriptyline Hydrochloride Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 50 mg of nortriptyline ($C_{19}H_{21}N$), add 50 mL of 0.1 mol/L hydrochloric acid TS, sonicate, and extract for 15 minutes while occasional shaking. Shake for 15 minutes, and add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Centrifuge this solution, pipet 2 mL of the supernatant liquid, add water to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 28 mg of nortriptyline hydrochloride for assay, previously dried at 105°C for 2 hours, and dissolve in 0.1 mol/L hydrochloric acid TS to make exactly 50 mL. Pipet 2 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the sample solution and standard solution at 239 nm as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, using diluted 0.1 mol/L hydrochloric acid TS (1 in 50) as the blank.

Amount (mg) of nortriptyline ($C_{19}H_{21}N$)
$= M_S \times A_T/A_S \times 2 \times 0.878$

M_S: Amount (mg) of nortriptyline hydrochloride for assay taken

Containers and storage Containers—Tight containers.

Pioglitazone Hydrochloride and Glimepiride Tablets

ピオグリタゾン塩酸塩·グリメピリド錠

Change the Identification (2) as follows:

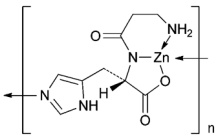
Identification

(2) Wash the membrane filter obtained in (1) with 100 mL of 0.1 mol/L hydrochloric acid TS, and extract with methanol so that each mL contains about 10 μg of glimepiride ($C_{24}H_{34}N_4O_5S$). Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 227 nm and 231 nm.

Add the following:

Polaprezinc

ポラプレジンク



$(C_9H_{12}N_4O_3Zn)_n$

catena-Poly{zinc-μ-[β-alanyl-L-histidinato(2-)-N,N^N,O:N^τ]}

[*107667-60-7*]

Polaprezinc contains not less than 98.0% and not more than 102.0% of polaprezinc ($C_9H_{12}N_4O_3Zn$: 289.60), and contains not less than 21.5% and not more than 23.0% of zinc (Zn: 65.38), calculated on the anhydrous basis.

Description Polaprezinc occurs as a white to pale yellow-white crystalline powder.

It is practically insoluble in water, in methanol and in ethanol (99.5).

It dissolves in dilute hydrochloric acid.

Identification **(1)** To 2 mL of a solution of Polaprezinc in 0.2 mol/L hydrochloric acid TS (1 in 1000) add 0.5 mL of a solution of sulfanilic acid in 1 mol/L hydrochloric acid TS (1 in 200), 0.5 mL of a solution of sodium nitrite (1 in 20) and 3 mL of sodium carbonate TS: a red color is produced.

(2) A solution of Polaprezinc in 0.2 mol/L hydrochloric acid TS (1 in 1000) responds to Qualitative Tests <*1.09*> for zinc salt.

(3) Determine the infrared absorption spectrum of Polaprezinc as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

Optical rotation <*2.49*> $[\alpha]_D^{20}$: +8 – +9° (1 g calculated on the anhydrous basis, 3 mol/L hydrochloric acid TS, 50 mL, 100 mm).

Purity **(1)** Lead—Weigh accurately about 0.5 g of Polaprezinc, dissolve in 3 mL of dilute nitric acid, add water to make exactly 10 mL, and use this solution as the sample solution. Separately, pipet 0.5 mL, 1.0 mL, 1.5 mL and 2.0 mL of Standard Lead Solution, to each solution add 3 mL of dilute nitric acid and water to make exactly 10 mL, and use these solutions as the standard solutions. Perform the test with the sample solution and standard solutions as directed under Atomic Absorption Spectrophotometry <*2.23*> according to the following conditions, and calculate the amount of lead in the sample solution using a calibration curve obtained from the absorbances of the standard solutions: not more than 10 ppm.

Gas: Combustible gas—Acetylene.
Supporting gas—Air.

Lamp: Lead hollow-cathode lamp.

Wavelength: 283.3 nm.

(2) Related substances—Dissolve 50 mg of Polaprezinc in 10 mL of 0.1 mol/L hydrochloric acid TS, add the mobile phase to make 100 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the peak area of L-histidine, having the relative retention time of about 0.38 to L-carnosine, obtained from the sample solution is not larger than 1/5 times of the peak area of L-carnosine from the standard solution, the area of the peak other than L-carnosine and the peak mentioned above from the sample solution is not larger than 1/10 times of the peak area of L-carnosine from the standard solution. Furthermore, the total area of the peaks other than L-carnosine from the sample solution is not larger than the peak area of L-carnosine from the standard solution.

Operating conditions—

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 4 times as long as the retention time of L-carnosine, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 2 mL of the standard solution, add the mobile phase to make exactly 20 mL. Confirm that the peak area of L-carnosine obtained with 10 μL of this solution is equivalent to 7 to 13% of that with 10 μL of the standard solution.

System performance: Dissolve 50 mg each of Polaprezinc and L-histidine in 10 mL of 0.1 mol/L hydrochloric acid TS, and add the mobile phase to make 100 mL. When the procedure is run with 10 μL of this solution under the above

operating conditions, L-histidine and L-carnosine are eluted in this order with the resolution between these peaks being not less than 12.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of L-carnosine is not more than 2.0%.

Water ⟨*2.48*⟩ Not more than 5.0% (0.2 g, volumetric titration, direct titration, stir for 30 minutes).

Assay **(1)** Polaprezinc—Weigh accurately about 25 mg of Polaprezinc, dissolve in 5 mL of 0.1 mol/L hydrochloric acid TS, add the mobile phase to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of L-Carnosine RS, previously dried at 105°C for 3 hours, dissolve in 5 mL of 0.1 mol/L hydrochloric acid TS, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions. Determine the peak areas, A_T and A_S, of L-carnosine in each solution.

$$\text{Amount (mg) of polaprezinc } (C_9H_{12}N_4O_3Zn) = M_S \times A_T/A_S \times 1.292$$

M_S: Amount (mg) of L-Carnosine RS taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45°C.

Mobile phase: Dissolve 1.4 g of potassium dihydrogen phosphate in 1000 mL of water, adjust to pH 3.5 with diluted phosphoric acid (1 in 100). Dissolve 2 g of sodium 1-octane sulfonate in 900 mL of this solution, and add 100 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of L-carnosine is about 15 minutes.

System suitability—

System performance: Dissolve 5 mg of L-histidine in 20 mL of the standard solution. When the procedure is run with 10 μL of this solution under the above operating conditions, L-histidine and L-carnosine are eluted in this order with the resolution between these peaks being not less than 12.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of L-carnosine is not more than 1.0%.

(2) Zinc—Weigh accurately about 0.2 g of Polaprezinc, dissolve in 3 mL of dilute hydrochloric acid, and add water to make exactly 100 mL. Pipet 25 mL of this solution, add 10 mL of ammonia-ammonium chloride buffer solution (pH 10.7), and titrate ⟨*2.50*⟩ with 0.01 mol/L disodium dihydrogen ethylenediamine tetraacetate VS (indicator: 40 mg of eriochrome black T-sodium chloride indicator).

Each mL of 0.01 mol/L disodium dihydrogen ethylenediamine tetraacetate VS
= 0.6538 mg Zn

Containers and storage Containers—Tight containers.

Add the following:

Polaprezinc Granules

ポラプレジンク顆粒

Polaprezinc Granules contain not less than 95.0% and not more than 105.0% of the labeled amount of polaprezinc $[(C_9H_{12}N_4O_3Zn)_n]$.

Method of preparation Prepare as directed under Granules, with Polaprezinc.

Identification **(1)** To a quantity of Polaprezinc Granules, equivalent to 20 mg of Polaprezinc, add 20 mL of 0.2 mol/L hydrochloric acid TS, shake for 10 minutes, centrifuge, and use the supernatant liquid as the sample solution. To 2 mL of the sample solution add 0.5 mL of a solution of sulfanilic acid in 1 mol/L hydrochloric acid TS (1 in 200), 0.5 mL of a solution of sodium nitrite (1 in 20) and 3 mL of sodium carbonate TS: a red color develops.

(2) The sample solution obtained in (1) responds to Qualitative Tests ⟨*1.09*⟩ for zinc salt.

Uniformity of dosage units ⟨*6.02*⟩ Perform the test according to the following method: Polaprezinc Granules in single-dose packages meet the requirement of the Content uniformity test.

To the total content of 1 package of Polaprezinc Granules add exactly V mL of 0.2 mol/L hydrochloric acid TS so that each mL contains about 5 mg of polaprezinc $[(C_9H_{12}N_4O_3Zn)_n]$, shake vigorously for 10 minutes, and centrifuge. Pipet 5 mL of the supernatant liquid, add exactly 5 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the sample solution. Then, proceed as directed in the Assay.

$$\text{Amount (mg) of polaprezinc } [(C_9H_{12}N_4O_3Zn)_n] = M_S \times Q_T/Q_S \times V/5 \times 1.292$$

M_S: Amount (mg) of L-Carnosine RS taken

Dissolution ⟨*6.10*⟩ When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 0.05 mol/L acetic acid-sodium acetate buffer solution (pH 4.0) as the dissolution medium, the dissolution rate in 15 minutes of Polaprezinc Granules is not less than 80%.

Start the test with an accurately weighed amount of Polaprezinc Granules, equivalent to about 75 mg of polaprezinc $[(C_9H_{12}N_4O_3Zn)_n]$, withdraw not less than 20

mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 10 mL of the first filtrate, pipet 1 mL of the subsequent filtrate, add diluted nitric acid (77 in 10,000) to make exactly 25 mL, and use this solution as the sample solution. Separately, pipet suitable volumes of Standard Zinc Stock Solution, to each solution add diluted nitric acid (77 in 10,000) so that each mL contains 0.4 to 0.8 μg of zinc (Zn: 65.38), and use these solutions as the standard solutions. Perform the test with the sample solution and standard solutions as directed under Atomic Absorption Spectrophotometry <2.23> according to the following conditions, and calculate the amount of zinc in the sample solution using a calibration curve obtained from the absorbances of the standard solutions.

Dissolution rate (%) with respect to the labeled amount of polaprezinc $[(C_9H_{12}N_4O_3Zn)_n]$

= Content (μg/mL) of zinc in the sample solution/M_T × 1/C × 2250 × 4.429

M_T: Amount (g) of Polaprezinc Granules taken
C: Labeled amount (mg) of polaprezinc $[(C_9H_{12}N_4O_3Zn)_n]$ in 1 g

Gas: Combustible gas—Acetylene.
Supporting gas—Air.
Lamp: Zinc hollow-cathode lamp.
Wavelength: 213.9 nm.

Assay Weigh accurately an amount of Polaprezinc Granules, equivalent to about 0.1 g of polaprezinc $[(C_9H_{12}N_4O_3Zn)_n]$, add exactly 20 mL of 0.2 mol/L hydrochloric acid TS, shake vigorously for 10 minutes, and centrifuge. Pipet 5 mL of the supernatant liquid, add exactly 5 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of L-Carnosine RS, previously dried at 105°C for 3 hours, dissolve in 5 mL of 0.2 mol/L hydrochloric acid TS, add exactly 5 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of L-carnosine to that of the internal standard.

Amount (mg) of polaprezinc $[(C_9H_{12}N_4O_3Zn)_n]$
= $M_S \times Q_T/Q_S \times 4 \times 1.292$

M_S: Amount (mg) of L-Carnosine RS taken

Internal standard solution—Dissolve 0.25 g of 4-aminoacetophenone in 5 mL of acetonitrile, and add the mobile phase to make 100 mL.

Operating conditions—

Proceed as directed in the operating conditions in the Assay (1) under Polaprezinc.

System suitability—

System performance: When the procedure is run with 5 μL of the standard solution under the above operating conditions, 4-aminoacetophenone and L-carnosine are eluted in this order with the resolution between these peaks being not less than 6.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of L-carnosine to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Add the following:

Ritodrine Hydrochloride Injection

リトドリン塩酸塩注射液

Ritodrine Hydrochloride Injection is an aqueous injection.

It contains not less than 95.0% and not more than 105.0% of the labeled amount of ritodrine hydrochloride ($C_{17}H_{21}NO_3$.HCl: 323.81).

Method of preparation Prepare as directed under Injections, with Ritodrine Hydrochloride.

Manufacture Ritodrine Hydrochloride Injection is produced by the formulation and the manufacturing method to ensure that the amounts of related substances do not exceed the limit values of related substances under Ritodrine Hydrochloride.

Description Ritodrine Hydrochloride Injection is a clear and colorless liquid.

Identification To a volume of Ritodrine Hydrochloride Injection, equivalent to 50 mg of Ritodrine Hydrochloride, add 0.01 mol/L hydrochloric acid TS to make 100 mL. To 10 mL of this solution add 0.01 mol/L hydrochloric acid TS to make 100 mL. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits a maximum between 272 nm and 276 nm.

pH Being specified separately when the drug is granted approval based on the Law.

Bacterial endotoxins <4.01> Less than 25 EU/mg.

Extractable volume <6.05> It meets the requirement.

Foreign insoluble matter <6.06> Perform the test according to Method 1: it meets the requirement.

Insoluble particulate matter <6.07> It meets the requirement.

Sterility <4.06> Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Pipet a volume of Ritodrine Hydrochloride Injection, equivalent to about 20 mg of ritodrine hydrochloride ($C_{17}H_{21}NO_3$.HCl), and add a mixture of 0.02 mol/L sodium dihydrogen phosphate dihydrate solution and methanol (7:3) to make exactly 250 mL, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of Ritodrine Hydrochloride RS, previously dried at 105°C for 2 hours, dissolve in a mixture of 0.02 mol/L sodium dihydrogen phosphate dihydrate solution and methanol (7:3) to make exactly 250 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine the peak areas, A_T and A_S, of ritodrine in each solution.

Amount (mg) of ritodrine hydrochloride ($C_{17}H_{21}NO_3$.HCl) $= M_S \times A_T/A_S$

M_S: Amount (mg) of Ritodrine Hydrochloride RS taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 6 mm in inside diameter and 15 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: Dissolve 6.6 g of diammonium hydrogen phosphate and 1.1 g of sodium 1-heptansulfonate in 840 mL of water, add 160 mL of acetonitrile for liquid chromatography, and adjust to pH 3.0 with phosphoric acid.

Flow rate: Adjust so that the retention time of ritodrine is about 19 minutes.

System Suitability—

System performance: Dissolve 10 mg of ritodrine hydrochloride in 50 mL of dilute sulfuric acid. Heat a portion of this solution in a water bath for about 30 minutes, and allow to cool. Measure a portion of this solution, and add the same volume of 2 mol/L sodium hydroxide TS. Dissolve 2 mg of ritodrine hydrochloride in 10 mL of this solution, and add a mixture of 0.02 mol/L sodium dihydrogen phosphate dihydrate solution and methanol (7:3) to make 25 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, ritodrine and ritodrine threo-isomer are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of ritodrine is not more than 1.0%.

Containers and storage Containers—Hermetic containers.

Storage—At a temperature between 2°C and 8°C.

Saccharin

サッカリン

Delete the description of harmonization in the beginning and symbols (◆ ◆) in the Description, Melting point, Purity (2) and (4), and Containers and storage.

Saccharin Sodium Hydrate

サッカリンナトリウム水和物

Delete the description of harmonization in the beginning and symbols (◆ ◆) in the Description, Purity (3) and (5), and Containers and storage.

Light Anhydrous Silicic Acid

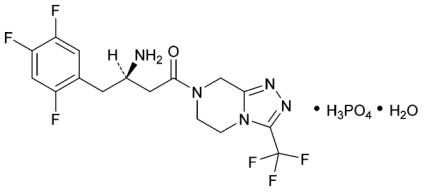
軽質無水ケイ酸

Delete the Volume test:

Add the following:

Sitagliptin Phosphate Hydrate

シタグリプチンリン酸塩水和物



$C_{16}H_{15}F_6N_5O.H_3PO_4.H_2O$: 523.32

(3*R*)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one monophosphate monohydrate [*654671-77-9*]

Sitagliptin Phosphate Hydrate contains not less than 98.0% and not more than 102.0% of sitagliptin phosphate ($C_{16}H_{15}F_6N_5O.H_3PO_4$: 505.31), calculated on the anhydrous basis.

Description Sitagliptin Phosphate Hydrate occurs as a white powder.

It is soluble in water, sparingly soluble in methanol, very slightly soluble in acetonitrile and in ethanol (99.5).

Identification (1) Determine the absorption spectrum of a solution of Sitagliptin Phosphate Hydrate (1 in 10,000) as directed under Ultraviolet-visible Spectrophotometry

<2.24>, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Sitagliptin Phosphate RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Sitagliptin Phosphate Hydrate as directed in the paste method under Infrared Spectrophotometry <2.25>, and compare the spectrum with the Reference Spectrum or the spectrum of Sitagliptin Phosphate RS: both spectra exhibit similar intensities of absorption at the same wave numbers. Alternatively, perform the test by the potassium bromide disk method or the ATR method, and compare the spectrum with the spectrum of Sitagliptin Phosphate RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) A solution of Sitagliptin Phosphate Hydrate (1 in 25) responds to Qualitative Tests <1.09> (1) for phosphate.

Purity **(1)** Heavy metals—Being specified separately when the drug is granted approval based on the Law.

(2) Related substances—Use the sample solution obtained in the Assay as the sample solution. Pipet 1 mL of the sample solution, add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 1000 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic integration method: the area of the peak other than sitagliptin obtained from the sample solution is not larger than the peak area of sitagliptin from the standard solution, and the total area of the peaks other than sitagliptin from the sample solution is not larger than 5 times the peak area of sitagliptin from the standard solution. For this calculation the peak area not larger than 1/2 times the peak area of sitagliptin from the standard solution is excluded.

Operating conditions—

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 5.5 times as long as the retention time of sitagliptin, beginning after the solvent peak.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 10 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the SN ratio of the peak of sitagliptin is not less than 10.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sitagliptin is not more than 2.0%.

(3) Enantiomer—Dissolve 80 mg of Sitagliptin Phosphate Hydrate in a mixture of methanol and water (9:1) to make 10 mL, and use this solution as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine the total peak area, A_T, of sitagliptin and related substance A (enantiomer), having the relative retention time of about 0.9 to sitagliptin and the peak area, A_S, of related substance A (enantiomer), and calculate the amount of the enantiomer by the following equation: not more than 0.5%.

$$\text{Amount (\%) of enantiomer} = A_S/A_T \times 100$$

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 268 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with amylose tris-(3,5-dimethylphenylcarbamate)-coated silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35°C.

Mobile phase: A mixture of ethanol (99.5), heptane, water and diethylamine (600:400:1:1).

Flow rate: 0.8 mL per minute.

System suitability—

Test for required detectability: Pipet 1 mL of the sample solution, and dissolve in a mixture of methanol and water (9:1) to make exactly 100 mL. Pipet 1 mL of this solution, add a mixture of methanol and water (9:1) to make exactly 10 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, the SN ratio of the peak of sitagliptin is not less than 10.

System performance: Dissolve 8 mg of Sitagliptin Phosphate RS for System Suitability in 1 mL of a mixture of methanol and water (9:1). When the procedure is run with 10 μL of this solution under the above operating conditions, the resolution between the peaks of related substance A (enantiomer) and sitagliptin is not less than 1.5.

Water <2.48> 3.3 – 3.7% (0.3 g, volumetric titration, direct titration).

Residue on ignition <2.44> Not more than 0.2% (1 g, platinum crucible).

Assay Weigh accurately about 20 mg each of Sitagliptin Phosphate Hydrate and Sitagliptin Phosphate RS (separately determine the water <2.48> in the same manner as Sitagliptin Phosphate Hydrate), dissolve each in a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 200 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of sitagliptin in each solution.

Amount (mg) of sitagliptin phosphate ($C_{16}H_{15}F_6N_5O.H_3PO_4$)
$= M_S \times A_T/A_S$

M_S: Amount (mg) of Sitagliptin Phosphate RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with cyanopropylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30°C.

Mobile phase: Dissolve 1.36 g of potassium dihydrogen phosphate in 900 mL of water, adjust to pH 2.0 with phosphoric acid, and add water to make 1000 mL. To 850 mL of this solution add 150 mL of acetonitrile for liquid chromatography.

Flow rate: 1.0 mL per minute.

System suitability—

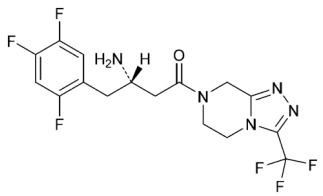
System performance: Place 10 mg of Sitagliptin Phosphate RS and 1 mg of sodium stearyl fumarate in a vial, and add 1 mL of water. Stopper the vial tightly, and heat at 80°C for 20 to 48 hours. Take out the contents of the vial, wash the vial 3 times with a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1), combine the washings and the content, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make 100 mL. Stir this solution for 1 hour, and centrifuge for 10 minutes or until the solution becomes clear. Use the supernatant liquid as the solution for system suitability test. When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the resolution between sitagliptin and the peak having the relative retention time of about 1.2 to sitagliptin is not less than 1.5.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sitagliptin is not more than 1.0%.

Containers and storage Containers—Tight containers.

Others

Related substance A (enantiomer):
(3*S*)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifuluorophenyl)butan-1-one



Add the following:

Sitagliptin Phosphate Tablets

シタグリプチンリン酸塩錠

Sitagliptin Phosphate Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of sitagliptin ($C_{16}H_{15}F_6N_5O$: 407.31).

Method of preparation Prepare as directed under Tablets, with Sitagliptin Phosphate Hydrate.

Manufacture The management strategy of Sitagliptin Phosphate Tablets is based on systematic development methods, which put emphasis on prior setting targets, understanding of products and processes, and process control, and which is based on quality risk management and proven science. In addition when it can be scientifically possible to explain that a disintegration test ensure quality with distinguishability equal or better than a dissolution test, the following disintegration is alternative for the estimation of dissolution.

Disintegration <*6.09*> Perform the test for 5 minutes: it meets the requirement.

Identification **(1)** To 1 tablet of Sitagliptin Phosphate Tablets add water so that each mL contains about 0.2 mg of sitagliptin ($C_{16}H_{15}F_6N_5O$), and shake thoroughly to disintegrate. Centrifuge this solution. Determine the absorption spectrum of the supernatant liquid as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 265 nm and 269 nm.

(2) Perform the test with 20 μL of the sample solution and standard solution obtained in the Assay as directed under Liquid Chromatography <*2.01*> according to the operating conditions in the Assay: the retention times of the principal peaks in the chromatograms obtained from the sample solution and the standard solution are the same.

Purity Related substances—Use the sample solution obtained in the Assay as the sample solution. Separately, pipet 1 mL of the standard solution obtained in the Assay, add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 500 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine the peak area, A_T, of related substance obtained from the sample solution and the peak area, A_S, of sitagliptin from the standard solution, and calculate the amount of related substances by the following equation: the total amount of related substances is not more than 0.2%. For this calculation the amount of related substance not more than 0.1% is excluded.

Amount (%) of related substance
$= M_S \times A_T/A_S \times V'/V \times 1/C \times 1/50 \times 0.806$

M_S: Amount (mg) of Sitagliptin Phosphate RS taken, cal-

culated on the anhydrous basis

V'/V: Dilution factor for the sample solution in the Assay

C: Labeled amount (mg) of sitagliptin ($C_{16}H_{15}F_6N_5O$) in 1 tablet

Operating conditions—

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 5.5 times as long as the retention time of sitagliptin, beginning after the solvent peak.

System suitability—

System performance and system repeatability: Proceed as directed in the system suitability in the Assay.

Test for required detectability: To 5 mL of the standard solution add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 10 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the SN ratio of the peak of sitagliptin is not less than 10.

Uniformity of dosage units ⟨*6.02*⟩ Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

To 1 tablet of Sitagliptin Phosphate Tablets add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 25 mL, and stir thoroughly. Pipet V mL of this solution, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly V' mL so that each mL contains about 80 μg of sitagliptin ($C_{16}H_{15}F_6N_5O$). Centrifuge this solution, and use the supernatant liquid as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of sitagliptin ($C_{16}H_{15}F_6N_5O$)
$= M_S \times A_T/A_S \times V'/V \times 1/10 \times 0.806$

M_S: Amount (mg) of Sitagliptin Phosphate RS taken, calculated on the anhydrous basis

Dissolution ⟨*6.10*⟩ When the test is performed at 100 revolutions per minute according to the Basket method, using 900 mL of water as the dissolution medium, the dissolution rate in 15 minutes of Sitagliptin Phosphate Tablets is not less than 85%.

Start the test with 1 tablet of Sitagliptin Phosphate Tablets, withdraw not less than 4 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size of 0.45 μm. Discard not less than 2 mL of the first filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 14 μg of sitagliptin ($C_{16}H_{15}F_6N_5O$), and use this solution as the sample solution. Separately, weigh accurately about 29 mg of Sitagliptin Phosphate RS (separately determine the water ⟨*2.48*⟩ in the same manner as Sitagliptin Phosphate Hydrate), and dissolve in a solution of sodium chloride (37 in 25,000) to make exactly 100 mL. Pipet 6 mL of this solution, and add a solution of sodium chloride (37 in 25,000) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine the peak areas, A_T and A_S, of sitagliptin in each solution.

Dissolution rate (%) with respect to the labeled amount of sitagliptin ($C_{16}H_{15}F_6N_5O$)
$= M_S \times A_T/A_S \times V'/V \times 1/C \times 54 \times 0.806$

M_S: Amount (mg) of Sitagliptin Phosphate RS taken, calculated on the anhydrous basis

C: Labeled amount (mg) of sitagliptin ($C_{16}H_{15}F_6N_5O$) in 1 tablet

Operating conditions—

Column, column temperature and flow rate: Proceed as directed in the operating conditions in the Assay.

Detector: An ultraviolet absorption photometer (wavelength: 267 nm).

Mobile phase: Dissolve 1.36 g of potassium dihydrogen phosphate in 900 mL of water, adjust to pH 2.0 with phosphoric acid, and add water to make 1000 mL. To 750 mL of this solution add 250 mL of acetonitrile for liquid chromatography.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of sitagliptin are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sitagliptin is not more than 1.0%.

Assay To 10 Sitagliptin Phosphate Tablets add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 250 mL, and stir thoroughly. Pipet V mL of this solution, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly V' mL so that each mL contains about 80 μg of sitagliptin ($C_{16}H_{15}F_6N_5O$). Centrifuge this solution, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 26 mg of Sitagliptin Phosphate RS (separately determine the water ⟨*2.48*⟩ in the same manner as Sitagliptin Phosphate Hydrate), dissolve in a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 250 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine the peak areas, A_T and A_S, of sitagliptin in each solution.

Amount (mg) of sitagliptin ($C_{16}H_{15}F_6N_5O$) in 1 tablet of Sitagliptin Phosphate Tablets

$= M_S \times A_T/A_S \times V'/V \times 1/10 \times 0.806$

M_S: Amount (mg) of Sitagliptin Phosphate RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with cyanopropylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30°C.

Mobile phase: Dissolve 1.36 g of potassium dihydrogen phosphate in 900 mL of water, adjust to pH 2.0 with phosphoric acid, and add water to make 1000 mL. To 850 mL of this solution add 150 mL of acetonitrile for liquid chromatography.

Flow rate: 1.0 mL per minute.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay under Sitagliptin Phosphate Hydrate. The following method can be applied when sodium stearyl fumarate is contained in the additive of the tablet.

Crush 1 tablet of Sitagliptin Phosphate Tablets, transfer to a vial, and add 1 mL of water. Stopper the vial tightly, and heat at 80°C for 20 to 48 hours. Take out the contents of the vial, wash the vial 3 times with a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1), combine the washings and the content, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make 100 mL. Stir this solution for 1 hour, and centrifuge for 10 minutes or until the solution becomes clear. When the procedure is run with 20 μL of the supernatant liquid under the above operating conditions, the resolution between sitagliptin and the peak having the relative retention time of about 1.2 to sitagliptin is not less than 1.5.

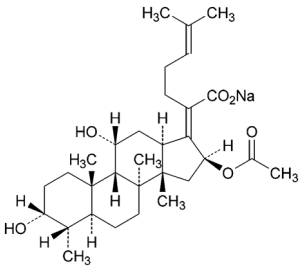
System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sitagliptin is not more than 1.0%.

Containers and storage Containers—Tight containers.

Sodium Fusidate

フシジン酸ナトリウム

Change the Structural formula as follows:



Change the purity as follows:

Purity **(1)** Heavy metals <*1.07*>—Proceed with 2.0 g of Sodium Fusidate according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Related substances—Dissolve 25 mg of Sodium Fusidate in a mixture of acetonitrile for liquid chromatography, diluted phosphoric acid (3 in 1000) and methanol (5:4:1) to make 10 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the peak area of related substance A, having the relative retention time of about 0.4 to fusidic acid, obtained from the sample solution is not larger than 3/10 times the peak area of fusidic acid from the standard solution, the peak area of related substance B, having the relative retention time of about 0.5, from the sample solution is not larger than 2/5 times the peak area of fusidic acid from the standard solution, the peak areas of related substance C having the relative retention time of about 0.6, related substance D having the relative retention time of about 0.63, an unknown substance having the relative retention time of about 0.65, related substance E having the relative retention time of about 0.7, related substance G having the relative retention time of about 0.96 and related substance H having the relative retention time of about 1.18, from the sample solution are not larger than 1/5 times the peak area of fusidic acid from the standard solution, the peak area of related substance F, having the relative retention time of about 0.82, from the sample solution is not larger than 7/10 times the peak area of fusidic acid from the standard solution, the peak area of related substance I, having the relative retention time of about 1.23, from the sample solution is not larger than 1/2 times the peak area of fusidic acid from the standard solution, the peak area of related substance J, having the relative retention time of about 1.4, from the sample solution is not larger than the peak area of

fusidic acid from the standard solution, the area of the peak other than fusidic acid and the peaks mentioned above from the sample solution is not larger than 1/10 times the peak area of fusidic acid from the standard solution. Furthermore, the total area of the peaks other than fusidic acid from the sample solution is not larger than 2 times the peak area of fusidic acid from the standard solution. For the areas of the peaks, related substances C, D, E, G and H, multiply their relative response factors, 0.7, 0.7, 0.3, 0.6 and 0.6, respectively.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3.5 μm in particle diameter).

Column temperature: A constant temperature of about 30°C.

Mobile phase A: A mixture of diluted phosphoric acid (3 in 1000), acetonitrile for liquid chromatography and methanol (2:2:1).

Mobile phase B: A mixture of acetonitrile for liquid chromatography, methanol and diluted phosphoric acid (3 in 1000) (7:2:1).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 3	100	0
3 – 28	100 → 0	0 → 100
28 – 33	0	100

Flow rate: 1.0 mL per minute.

Time span of measurement: For 33 minutes after injection, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 1 mL of the standard solution, and add a mixture of acetonitrile for liquid chromatography, diluted phosphoric acid (3 in 1000) and methanol (5:4:1) to make exactly 20 mL. Confirm that the peak area of fusidic acid obtained with 20 μL of this solution is equivalent to 3.5 to 6.5% of that with 20 μL of the standard solution.

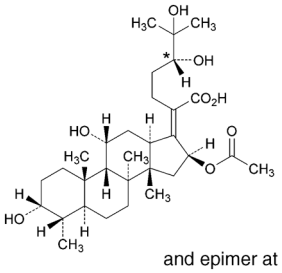
System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of fusidic acid are not less than 43,000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of fusidic acid is not more than 2.0%.

Add the following next to the Containers and storage:

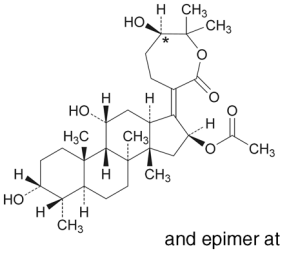
Others

Related substance A:
(24*RS*,17*Z*)-*ent*-16α-Acetoxy-3β,11β,24,25-tetrahydroxy-4β,8β,14α-trimethyl-18-nor-5β,10α-cholest-17(20)-en-21-oic acid



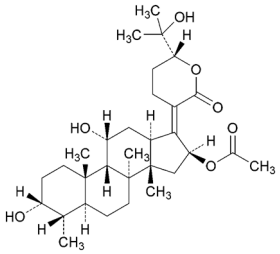
and epimer at C*

Related substance B:
(17*Z*)-*ent*-3β,11β-Dihydroxy-17-[(6*SR*)-6-hydroxy-7,7-dimethyl-2-oxooxepan-3-ylidene]-4β,8β,14α-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate

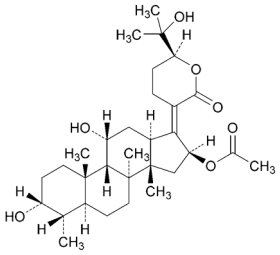


and epimer at C*

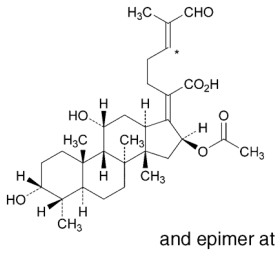
Related substance C:
(17*Z*)-*ent*-3β,11β-Dihydroxy-17-[(6*S*)-6-(2-hydroxypropan-2-yl)-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene]-4β,8β,14α-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate



Related substance D:
(17*Z*)-*ent*-3β,11β-Dihydroxy-17-[(6*R*)-6-(2-hydroxypropan-2-yl)-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene]-4β,8β,14α-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate

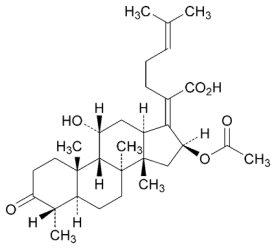


Related substance E:
(17*Z*,24*EZ*)-*ent*-16α-Acetoxy-3β,11β-dihydroxy-4β,8β,14α-trimethyl-26-oxo-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid

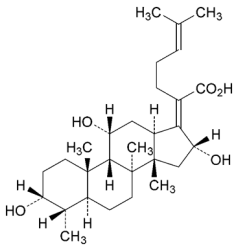


and epimer at C*

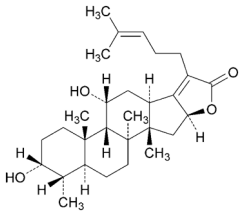
Related substance F:
(17*Z*)-*ent*-16α-Acetoxy-11β-hydroxy-4β,8β,14α-trimethyl-3-oxo-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid



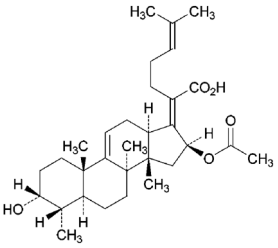
Related substance G:
(17*Z*)-*ent*-3β,11β,16β-Trihydroxy-4β,8β,14α-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid



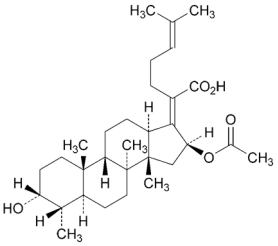
Related substance H:
(17*Z*)-*ent*-3β,11β-Dihydroxy-4β,8β,14α-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dieno-21,16α-lactone



Related substance I:
(17*Z*)-*ent*-16α-Acetoxy-3β-hydroxy-4β,8β,14α-trimethyl-18-nor-5β,10α-cholesta-9(11),17(20),24-trien-21-oic acid



Related substance J:
(17*Z*)-*ent*-16α-Acetoxy-3β-hydroxy-4β,8β,14α-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid



Add the following:

Sodium Valproate Extended-release Tablets A

バルプロ酸ナトリウム徐放錠 **A**

Sodium Valproate Extended-release Tablets A contain not less than 95.0% and not more than 105.0% of the labeled amount of sodium valproate ($C_8H_{15}NaO_2$: 166.19).

Method of preparation Prepare as directed under Tablets, with Sodium Valproate.

Identification To a quantity of powdered Sodium Valproate Extended-release Tablets A, equivalent to 0.2 g of Sodium Valproate, add 20 mL of water, shake thoroughly, and centrifuge. To 2 mL of the supernatant liquid add 1 mL of a solution of cobalt (II) nitrate hexahydrate (1 in 20), and heat on a water bath: a purple precipitate is formed.

Uniformity of dosage units ⟨*6.02*⟩ Perform the test according to the following method: it meets the requirement of the Content uniformity test.

Crush 1 tablet of Sodium Valproate Extended-release Tablets A, add exactly *V*/40 mL of the internal standard solution, add 4*V*/5 mL of a mixture of methanol and water (3:2), shake vigorously, add a mixture of methanol and water (3:2) to make *V* mL so that each mL contains about 1 mg of sodium valproate ($C_8H_{15}NaO_2$), and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 5 mL of the filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 0.1 g of sodium valproate for assay, previously dried at 105°C for 3 hours, add exactly 2.5 mL of the internal standard solution, add a mixture of methanol and water

(3:2) to make 100 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay.

$$\text{Amount (mg) of sodium valproate } (C_8H_{15}NaO_2) = M_S \times Q_T/Q_S \times V/100$$

M_S: Amount (mg) of sodium valproate for assay taken

Internal standard solution—A solution of ethyl parahydroxybenzoate in a mixture of methanol and water (3:2) (1 in 5000).

Dissolution ⟨*6.10*⟩ When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rates of a 100-mg tablet in 4 hours, in 6 hours and in 12 hours are 15 to 45%, 40 to 70%, and not less than 75%, respectively, and those of a 200-mg tablet in 4 hours, in 6 hours and in 12 hours are 15 to 45%, 35 to 65%, and not less than 75%, respectively.

Start the test with 1 tablet of Sodium Valproate Extended-release Tablets A, withdraw exactly 20 mL of the medium at the specified minutes after starting the test and supply exactly 20 mL of water warmed to 37 ± 0.5°C immediately after withdrawing of the medium every time. Filter the media through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 10 mL of the first filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 0.11 mg of sodium valproate ($C_8H_{15}NaO_2$), and use these solutions as the sample solutions. Separately, weigh accurately about 56 mg of sodium valproate for assay, previously dried at 105°C for 3 hours, and dissolve in water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 50 μL each of the sample solutions and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine the peak areas, $A_{T(n)}$ and A_S, of valproic acid in each solution.

$$\text{Dissolution rate (\%) with respect to the labeled amount of sodium valproate } (C_8H_{15}NaO_2) \text{ on the } n\text{th medium withdrawing } (n = 1, 2, 3) = M_S \times \left\{ \frac{A_{T(n)}}{A_S} + \sum_{i=1}^{n-1} \left(\frac{A_{T(i)}}{A_S} \times \frac{1}{45} \right) \right\} \times \frac{V'}{V} \times \frac{1}{C} \times 180$$

M_S: Amount (mg) of sodium valproate for assay taken

C: Labeled amount (mg) of sodium valproate ($C_8H_{15}NaO_2$) in 1 tablet

Operating conditions—

Proceed as directed in the operating conditions in the Assay.

System suitability—

System performance: When the procedure is run with 50 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of valproic acid are not less than 3000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 50 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of valproic acid is not more than 1.5%.

Assay Weigh accurately the mass of not less than 20 Sodium Valproate Extended-release Tablets A, and powder. Weigh accurately a portion of the powder, equivalent to about 0.1 g of sodium valproate ($C_8H_{15}NaO_2$), add about 80 mL of the mobile phase, shake thoroughly, add the mobile phase to make exactly 100 mL, and centrifuge. Pipet 20 mL of the supernatant liquid, add exactly 5 mL of the internal standard solution, and use this solution as the sample solution. Separately, weigh accurately about 0.1 g of sodium valproate for assay, previously dried at 105°C for 3 hours, dissolve in the mobile phase to make exactly 100 mL. Pipet 20 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of valproic acid to that of the internal standard.

$$\text{Amount (mg) of sodium valproate } (C_8H_{15}NaO_2) = M_S \times Q_T/Q_S$$

M_S: Amount (mg) of sodium valproate for assay taken

Internal standard solution—A solution of ethyl parahydroxybenzoate in the mobile phase (1 in 50,000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of 0.05 mol/L sodium dihydrogen phosphate TS (pH 3.0) and acetonitrile for liquid chromatography (1:1).

Flow rate: Adjust so that the retention time of valproic acid is about 6 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the internal standard and valproic acid are eluted in this order with the resolution between these peaks being not less than 7.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of valproic acid to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Add the following:

Sodium Valproate Extended-release Tablets B

バルプロ酸ナトリウム徐放錠 **B**

Sodium Valproate Extended-release Tablets B contain not less than 95.0% and not more than 105.0% of the labeled amount of sodium valproate ($C_8H_{15}NaO_2$: 166.19).

Method of preparation Prepare as directed under Tablets, with Sodium Valproate.

Identification To a quantity of the powdered Sodium Valproate Extended-release Tablets B, equivalent to 1.0 g of Sodium Valproate, add 10 mL of water, heat on a water bath for 30 minutes, and filter. To 2.5 mL of the filtrate add 2.5 mL of water and 1 mL of a solution of cobalt (II) nitrate hexahydrate (1 in 20), and heat on a water bath: a purple precipitate is formed.

Uniformity of dosage units ⟨*6.02*⟩ Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

To 1 tablet of Sodium Valproate Extended-release Tablets B add 150 mL of the mobile phase, allow to stand for not less than 16 hours, shake until the film is disintegrated, and add the mobile phase to make exactly 200 mL. Pipet V mL of this solution, and add the mobile phase to make exactly V' mL so that each mL contains about 1 mg of sodium valproate ($C_8H_{15}NaO_2$). Centrifuge this solution, and filter the supernatant liquid through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 5 mL of the filtrate, pipet 20 mL of the subsequent filtrate, add exactly 5 mL of the internal standard solution, and use this solution as the sample solution. Then, proceed as directed in the Assay.

$$\text{Amount (mg) of sodium valproate } (C_8H_{15}NaO_2) = M_S \times Q_T/Q_S \times V'/V \times 2$$

M_S: Amount (mg) of sodium valproate for assay taken

Internal standard solution—A solution of methyl parahydroxybenzoate in the mobile phase (1 in 50,000).

Dissolution ⟨*6.10*⟩ When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rates of a 200-mg tablet in 8 hours, in 11 hours and in 20 hours are 15 to 45%, 35 to 65%, and not less than 70%, respectively, and those of a 400-mg tablet in 9 hours, in 12 hours and in 21 hours are 15 to 45%, 35 to 65%, and not less than 70%, respectively.

Start the test with 1 tablet of Sodium Valproate Extended-release Tablets B, withdraw exactly 20 mL of the medium at the specified minutes after starting the test and supply exactly 20 mL of water warmed to 37 ± 0.5°C immediately after withdrawing of the medium every time. Filter the media through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 2 mL of the first filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 0.22 mg of sodium valproate ($C_8H_{15}NaO_2$), and use these solutions as the sample solutions. Separately, weigh accurately about 55 mg of sodium valproate for assay, previously dried at 105°C for 3 hours, dissolve in water to make exactly 250 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solutions and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine the peak areas, $A_{T(n)}$ and A_S, of valproic acid in each solution.

Dissolution rate (%) with respect to the labeled amount of sodium valproate ($C_8H_{15}NaO_2$) on the nth medium withdrawing (n = 1, 2, 3)

$$= M_S \times \left\{ \frac{A_{T(n)}}{A_S} + \sum_{i=1}^{n-1} \left(\frac{A_{T(i)}}{A_S} \times \frac{1}{45} \right) \right\} \times \frac{V'}{V} \times \frac{1}{C} \times 360$$

M_S: Amount (mg) of sodium valproate for assay taken

C: Labeled amount (mg) of sodium valproate ($C_8H_{15}NaO_2$) in 1 tablet

Operating conditions—

Proceed as directed in the operating conditions in the Assay.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of valproic acid are not less than 3000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of valproic acid is not more than 1.0%.

Assay To 20 Sodium Valproate Extended-release Tablets B add 150 mL of the mobile phase, allow to stand for not less than 16 hours, shake until the film is disintegrated, and add the mobile phase to make exactly 200 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly V mL so that each mL contains about 1 mg of sodium valproate ($C_8H_{15}NaO_2$). Centrifuge this solution, and filter the supernatant liquid through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 5 mL of the filtrate, pipet 20 mL of the subsequent filtrate, add exactly 5 mL of the internal standard solution, and use this solution as the sample solution. Separately, weigh accurately about 0.1 g of sodium valproate for assay, previously dried at 105°C for 3 hours, dissolve in the mobile phase to make exactly 100 mL. Pipet 20 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of valproic acid to that of the internal standard.

Amount (mg) of sodium valproate ($C_8H_{15}NaO_2$) in 1 tablet = $M_S \times Q_T/Q_S \times V/50$

M_S: Amount (mg) of sodium valproate for assay taken

Internal standard solution—A solution of methyl parahydroxybenzoate in the mobile phase (1 in 50,000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of 0.05 mol/L sodium dihydrogen phosphate TS (pH 3.0) and acetonitrile for liquid chromatography (1:1).

Flow rate: Adjust so that the retention time of valproic acid is about 6 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the internal standard and valproic acid are eluted in this order with the resolution between these peaks being not less than 7.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of valproic acid to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Teicoplanin

テイコプラニン

Change the Purity (4) as follows:

Purity

(4) Arsenic <*1.11*>—Prepare the test solution with 1.0 g of Teicoplanin according to Method 3, and perform the test (not more than 2 ppm).

Add the following:

Telmisartan and Hydrochlorothiazide Tablets

テルミサルタン·ヒドロクロロチアジド錠

Telmisartan and Hydrochlorothiazide Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$: 514.62) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$: 297.74).

Method of preparation Prepare as directed under Tablets, with Telmisartan and Hydrochlorothiazide.

Identification (1) Perform the test with 5 μL each of the sample solution and standard solution obtained in the Assay (1) as directed under Liquid Chromatography <*2.01*> according to the following conditions: the retention times of the peaks of telmisartan in the chromatograms obtained from the sample solution and standard solution are the same, and absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

Operating conditions—

Column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay (1).

Detector: A photodiode array detector (wavelength: 270 nm, spectrum range of measurement: 210 – 400 nm).

System suitability—

System performance: Proceed as directed in the system suitability in the Assay (1).

(2) Perform the test with 5 μL each of the sample solution and standard solution obtained in the Assay (2) as directed under Liquid Chromatography <*2.01*> according to the following conditions: the retention times of the peaks of hydrochlorothiazide in the chromatograms obtained from the sample solution and standard solution are the same, and absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

Operating conditions—

Column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay (1).

Detector: A photodiode array detector (wavelength: 270 nm, spectrum range of measurement: 210 – 400 nm).

System suitability—

System performance: Proceed as directed in the system suitability in the Assay (2).

Purity Related substances—To a quantity of powdered Telmisartan and Hydrochlorothiazide Tablets, equivalent to 12.5 mg of Hydrochlorothiazide, add 40 mL of the dissolving solution, disperse by sonicating, add the dissolving solution to make exactly 50 mL. Centrifuge this solution, and use the supernatant liquid as the sample solution. Pipet 1 mL of the sample solution, add the dissolving solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine each peak area by the automatic integration method: the area of the peak having the relative retention time of about 0.9 to hydrochlorothiazide, obtained from the sample solution is not larger than the peak area of hydrochlorothiazide from the standard solution.

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000

mL of acetonitrile.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column 4.0 mm in inside diameter and 15 cm in length, packed with octylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase A: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 3.5 with phosphoric acid.

Mobile phase B: Acetonitrile.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 8	90 → 50	10 → 50
8 – 12	50	50
12 – 18	50 → 20	50 → 80
18 – 20	20	80

Flow rate: 1.0 mL per minute.

System suitability—

Test for required detectability: Pipet 5 mL of the standard solution and add the dissolving solution to make exactly 50 mL. Confirm that the peak area of hydrochlorothiazide obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of hydrochlorothiazide are not less than 6000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 2.0%.

Uniformity of dosage units ⟨*6.02*⟩ Perform the test according to the following method: it meets the requirement of the Content uniformity test.

(1) Telmisartan—To 1 tablet of Telmisartan and Hydrochlorothiazide Tablets add $4V/5$ mL of the dissolving solution, disintegrate by sonicating, add the dissolving solution to make exactly V mL so that each mL contains about 1.6 mg of telmisartan ($C_{33}H_{30}N_4O_2$). Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Proceed as directed in the Assay (1).

$$\text{Amount (mg) of telmisartan } (C_{33}H_{30}N_4O_2) = M_S \times A_T/A_S \times V/50$$

M_S: Amount (mg) of telmisartan for assay taken

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

(2) Hydrochlorothiazide—To 1 tablet of Telmisartan and Hydrochlorothiazide Tablets add $4V/5$ mL of the dissolving solution, disintegrate by sonicating, add the dissolving solution to make exactly V mL so that each mL contains about 0.25 mg of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$). Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Proceed as directed in the Assay (2).

$$\text{Amount (mg) of hydrochlorothiazide } (C_7H_8ClN_3O_4S_2) = M_S \times A_T/A_S \times V/50$$

M_S: Amount (mg) of Hydrochlorothiazide RS taken

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

Dissolution ⟨*6.10*⟩ (1) Telmisartan—When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rates in 45 minutes of a telmisartan 40-mg and hydrochlorothiazide 12.5-mg tablet and a telmisartan 80-mg and hydrochlorothiazide 12.5-mg tablet are not less than 85% and not less than 80%, respectively.

Start the test with 1 tablet of Telmisartan and Hydrochlorothiazide Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 15 mL of the first filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL so that each mL contains about 44 μg of telmisartan ($C_{33}H_{30}N_4O_2$), and use this solution as the sample solution. Separately, weigh accurately about 44 mg of telmisartan for assay, previously dried at 105°C for 4 hours, dissolve in 10 mL of a solution of meglumine in methanol (1 in 250), and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 25 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine the peak areas, A_T and A_S, of telmisartan in each solution.

$$\text{Dissolution rate (\%) with respect to the labeled amount of telmisartan } (C_{33}H_{30}N_4O_2) = M_S \times A_T/A_S \times V'/V \times 1/C \times 90$$

M_S: Amount (mg) of telmisartan for assay taken
C: Labeled amount (mg) of telmisartan ($C_{33}H_{30}N_4O_2$) in 1 tablet

Operating conditions—

Proceed as directed in the operating conditions in the Assay (1).

System suitability—

System performance: When the procedure is run with 25 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of telmisartan are not less than 25,000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 25 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of telmisartan is not more than 2.0%.

(2) Hydrochlorothiazide—When the test is performed at 75 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rate in 45 minutes of Telmisartan and Hydrochlorothiazide Tablets is not less than 80%.

Start the test with 1 tablet of Telmisartan and Hydrochlorothiazide Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 15 mL of the first filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL so that each mL contains about 14 μg of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$), and use this solution as the sample solution. Separately, weigh accurately about 14 mg of Hydrochlorothiazide RS, previously dried at 105°C for 2 hours, and dissolve in methanol to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 25 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of hydrochlorothiazide in each solution.

Dissolution rate (%) with respect to the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$)

$$= M_S \times A_T/A_S \times V'/V \times 1/C \times 90$$

M_S: Amount (mg) of Hydrochlorothiazide RS taken
C: Labeled amount (mg) of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in 1 tablet

Operating conditions—

Proceed as directed in the operating conditions in the Assay (1).

System suitability—

System performance: When the procedure is run with 25 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of hydrochlorothiazide are not less than 1000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 25 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 2.0%.

Assay **(1)** Telmisartan—Weigh accurately the mass of not less than 20 Telmisartan and Hydrochlorothiazide Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 80 mg of telmisartan ($C_{33}H_{30}N_4O_2$), add 40 mL of the dissolving solution, sonicate, and add the dissolving solution to make exactly 50 mL. Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Separately, weigh accurately about 80 mg of telmisartan for assay, previously dried at 105°C for 4 hours, and dissolve in the dissolving solution to make exactly 50 mL. Pipet 5 mL of this solution, add the buffer solution to make exactly 25 mL, and use this solution as the standard solution. Perform the test with exactly 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of telmisartan in each solution.

Amount (mg) of telmisartan ($C_{33}H_{30}N_4O_2$)

$$= M_S \times A_T/A_S$$

M_S: Amount (mg) of telmisartan for assay taken

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 7.5 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase A: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 3.5 with phosphoric acid.

Mobile phase B: Acetonitrile.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 2	90	10
2 – 7	90 → 20	10 → 80
7 – 8	20	80

Flow rate: 0.8 mL per minute.

System suitability—

System performance: When the procedure is run with 5

μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of telmisartan are not less than 15,000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of telmisartan is not more than 1.0%.

(2) Hydrochlorothiazide—Weigh accurately the mass of not less than 20 Telmisartan and Hydrochlorothiazide Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 12.5 mg of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$), add 40 mL of the dissolving solution, sonicate, and add the dissolving solution to make exactly 50 mL. Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Separately, weigh accurately about 12.5 mg of Hydrochlorothiazide RS, previously dried at 105°C for 2 hours, and dissolve in the dissolving solution to make exactly 50 mL. Pipet 5 mL of this solution, add the buffer solution to make exactly 25 mL, and use this solution as the standard solution. Perform the test with exactly 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of hydrochlorothiazide in each solution.

Amount (mg) of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) $= M_S \times A_T/A_S$

M_S: Amount (mg) of Hydrochlorothiazide RS taken

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

Operating conditions—

Proceed as directed in the operating conditions in (1).

System suitability—

System performance: When the procedure is run with 5 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of hydrochlorothiazide are not less than 1500 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 1.0%.

Containers and storage Containers—Tight containers.

Testosterone Enanthate

テストステロンエナント酸エステル

Change the Description and Optical rotation as follows:

Description Testosterone Enanthate occurs as white to pale yellow, crystals or crystalline powder, or a pale yellow-brown viscous liquid. It is odorless or has a slight, characteristic odor.

It is freely soluble in ethanol (99.5), and practically insoluble in water.

Melting point: about 36°C

Optical rotation <2.49> $[\alpha]_D^{25}$: +76 – +86° (after drying, 0.1 g, ethanol (99.5), 10 mL, 100 mm).

Delete the following Monograph:

Freeze-dried Tetanus Antitoxin, Equine

乾燥破傷風ウマ抗毒素

Tipepidine Hibenzate Tablets

チペピジンヒベンズ酸塩錠

Change the Identification (2) as follows:

Identification

(2) To a quantity of powdered Tipepidine Hibenzate Tablets, equivalent to 11 mg of Tipepidine Hibenzate, add 30 mL of ethanol (99.5), and warm for 10 minutes with occasional shaking. After cooling, add ethanol (99.5) to make 50 mL, and filter. To 1 mL of the filtrate add ethanol (99.5) to make 20 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits a maximum between 280 nm and 286 nm.

Triamcinolone Acetonide

トリアムシノロンアセトニド

Change the Description and Optical rotation as follows:

Description Triamcinolone Acetonide occurs as a white crystalline powder.

It is sparingly soluble in ethanol (99.5) and in acetone, slightly soluble in methanol, and practically insoluble in water.

Melting point: about 290°C (with decomposition).

It shows crystal polymorphism.

Optical rotation ⟨*2.49*⟩ $[\alpha]_D^{25}$: +110 – +120° (after drying, 0.1 g, ethanol (99.5), 10 mL, 100 mm).

Ursodeoxycholic Acid

ウルソデオキシコール酸

Change the Melting point as follows:

Melting point ⟨*2.60*⟩ 201 – 205°C

Add the following:

Valsartan and Hydrochlorothiazide Tablets

バルサルタン·ヒドロクロロチアジド錠

Valsartan and Hydrochlorothiazide Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$: 435.52) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$: 297.74).

Method of preparation Prepare as directed under Tablets, with Valsartan and Hydrochlorothiazide.

Identification **(1)** To a quantity of powdered Valsartan and Hydrochlorothiazide Tablets, equivalent to 80 mg of Valsartan, add 5 mL of acetone, shake, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 16 mg of valsartan in 1 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography ⟨*2.03*⟩. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, hexane and acetic acid (100) (15:5:2) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): one of the two spots obtained from the sample solution and the spot from the standard solution show the same *R*f value.

(2) To a quantity of powdered Valsartan and Hydrochlorothiazide Tablets, equivalent to 6.25 mg of Hydrochlorothiazide, add 5 mL of acetone, shake, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 12.5 mg of hydrochlorothiazide in 10 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography ⟨*2.03*⟩. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, hexane and acetic acid (100) (15:5:2) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): one of the two spots obtained from the sample solution and the spot from the standard solution show the same *R*f value.

Uniformity of dosage units ⟨*6.02*⟩ (1) Valsartan—Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

To 1 tablet of Valsartan and Hydrochlorothiazide Tablets add 10 mL of water, and shake until the tablet is disintegrated. Add 10 mL of acetonitrile, shake thoroughly, and add a mixture of water and acetonitrile (1:1) to make exactly 50 mL. Centrifuge this solution, pipet V mL of the supernatant liquid, add a mixture of water and acetonitrile (1:1) to make exactly V' mL so that each mL contains about 0.4 mg of valsartan ($C_{24}H_{29}N_5O_3$), and use this solution as the sample solution. Proceed as directed in the Assay (1).

$$\text{Amount (mg) of valsartan } (C_{24}H_{29}N_5O_3) = M_S \times A_T/A_S \times V'/V \times 1/2$$

M_S: Amount (mg) of Valsartan RS taken, calculated on the anhydrous and residual solvent-free basis

(2) Hydrochlorothiazide—Perform the test according to the following method: it meets the requirement of the Content uniformity test.

To 1 tablet of Valsartan and Hydrochlorothiazide Tablets add 10 mL of water, and shake until the tablet is disintegrated. Add 10 mL of acetonitrile, shake thoroughly, and add a mixture of water and acetonitrile (1:1) to make exactly 50 mL. Centrifuge this solution, pipet V mL of the supernatant liquid, add a mixture of water and acetonitrile (1:1) to make exactly V' mL so that each mL contains about 31 μg of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$), and use this solution as the sample solution. Proceed as directed in the Assay (2).

$$\text{Amount (mg) of hydrochlorothiazide } (C_7H_8ClN_3O_4S_2) = M_S \times A_T/A_S \times V'/V \times 1/8$$

M_S: Amount (mg) of Hydrochlorothiazide RS taken

Dissolution ⟨*6.10*⟩ (1) Valsartan—When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rate in 30 minutes of Valsartan and Hydrochlorothiazide Tablets is not less than 75%.

Start the test with 1 tablet of Valsartan and Hydrochlorothiazide Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 5 mL of the first filtrate, pipet V mL of the subsequent filtrate, and add water to make exactly V' mL so that each mL contains about 89 μg of valsartan ($C_{24}H_{29}N_5O_3$). Pipet 5 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 45 mg of Valsartan RS (separately determine the water ⟨*2.48*⟩ and the residual solvent in the same manner as Valsartan), and dissolve in methanol to make exactly 50 mL. Pipet 10 mL of this solution, add exactly 100 mL of water, then add

methanol to make exactly 200 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of valsartan in each solution.

Dissolution rate (%) with respect to the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$)

$= M_S \times A_T/A_S \times V'/V \times 1/C \times 180$

M_S: Amount (mg) of Valsartan RS taken, calculated on the anhydrous and residual solvent-free basis

C: Labeled amount (mg) of valsartan ($C_{24}H_{29}N_5O_3$) in 1 tablet

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: Dissolve 14.68 g of disodium hydrogen phosphate dodecahydrate and 3.81 g of potassium dihydrogen phosphate in 1000 mL of water. To 4 volumes of this solution add 1 volume of acetonitrile.

Flow rate: Adjust so that the retention time of valsartan is about 6 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of valsartan are not less than 500, and not less than 0.7 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of valsartan is not more than 1.0%.

(2) Hydrochlorothiazide—When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rate in 15 minutes of Valsartan and Hydrochlorothiazide Tablets is not less than 85%.

Start the test with 1 tablet of Valsartan and Hydrochlorothiazide Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 5 mL of the filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 6.9 μg of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$), and use this solution as the sample solution. Separately, weigh accurately about 14 mg of Hydrochlorothiazide RS, previously dried at 105°C for 2 hours, and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of hydrochlorothiazide in each solution.

Dissolution rate (%) with respect to the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$)

$= M_S \times A_T/A_S \times V'/V \times 1/C \times 45$

M_S: Amount (mg) of Hydrochlorothiazide RS taken

C: Labeled amount (mg) of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in 1 tablet

Operating conditions—

Proceed as directed in the operating conditions in (1).

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of hydrochlorothiazide are not less than 3000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 1.0%.

Assay **(1)** Valsartan—Weigh accurately the mass of not less than 20 tablets of Valsartan and Hydrochlorothiazide Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 80 mg of valsartan ($C_{24}H_{29}N_5O_3$), add 10 mL of water, and shake. Add 10 mL of acetonitrile, shake thoroughly, add a mixture of water and acetonitrile (1:1) to make exactly 50 mL, and centrifuge. Pipet 5 mL of the supernatant liquid, add a mixture of water and acetonitrile (1:1) to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 40 mg of Valsartan RS (separately determine the water <2.48> and the residual solvent in the same manner as Valsartan), dissolve in a mixture of water and acetonitrile (1:1) to make exactly 25 mL, and use this solution as the valsartan standard stock solution. Pipet 5 mL of the valsartan standard stock solution, add a mixture of water and acetonitrile (1:1) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of valsartan in each solution.

Amount (mg) of valsartan ($C_{24}H_{29}N_5O_3$)

$= M_S \times A_T/A_S \times 2$

M_S: Amount (mg) of Valsartan RS taken, calculated on the anhydrous and residual solvent-free basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 271 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 12.5 cm in length, packed with octadecylsilanized

silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase A: A mixture of water, acetonitrile and trifluoroacetic acid (900:100:1).

Mobile phase B: A mixture of acetonitrile, water and trifluoroacetic acid (900:100:1).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 25	90 → 10	10 → 90

Flow rate: Adjust so that the retention time of valsartan is about 16 minutes.

System suitability—

System performance: Dissolve 1 mg of 4-amino-6-chlorobenzene-1,3-disulfonamide in a mixture of water and acetonitrile (1:1) to make 200 mL. To 1 mL of this solution, 5 mL of the valsartan standard stock solution and 5 mL of the hydrochlorothiazide standard stock solution in (2) add a mixture of water and acetonitrile (1:1) to make 20 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, 4-amino-6-chlorobenzene-1,3-disulfonamide, hydrochlorothiazide and valsartan are eluted in this order with the resolution between the peaks of 4-amino-6-chlorobenzene-1,3-disulfonamide and hydrochlorothiazide being not less than 1.5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of valsartan is not more than 1.0%.

(2) Hydrochlorothiazide—Weigh accurately the mass of not less than 20 tablets of Valsartan and Hydrochlorothiazide Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 6.25 mg of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$), add 10 mL of water, and shake. Add 10 mL of acetonitrile, shake thoroughly, add a mixture of water and acetonitrile (1:1) to make exactly 50 mL, and centrifuge. Pipet 5 mL of the supernatant liquid, add a mixture of water and acetonitrile (1:1) to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 12.5 mg of Hydrochlorothiazide RS, previously dried at 105°C for 2 hours, and dissolve in a mixture of water and acetonitrile (1:1) to make exactly 50 mL, and use this solution as the hydrochlorothiazide standard stock solution. Pipet 2.5 mL of the hydrochlorothiazide standard stock solution, add a mixture of water and acetonitrile (1:1) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of hydrochlorothiazide in each solution.

Amount (mg) of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) $= M_S \times A_T/A_S \times 1/2$

M_S: Amount (mg) of Hydrochlorothiazide RS taken

Operating conditions—

Proceed as directed in the operating conditions in (1).

System suitability—

System performance: Dissolve 1 mg of 4-amino-6-chlorobenzene-1,3-disulfonamide in a mixture of water and acetonitrile (1:1) to make 200 mL. To 1 mL of this solution, 5 mL of the valsartan standard stock solution in (1) and 5 mL of the hydrochlorothiazide standard stock solution add a mixture of water and acetonitrile (1:1) to make 20 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, 4-amino-6-chlorobenzene-1,3-disulfonamide, hydrochlorothiazide and valsartan are eluted in this order with the resolution between the peaks of 4-amino-6-chlorobenzene-1,3-disulfonamide and hydrochlorothiazide being not less than 1.5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 1.0%.

Add the following:

Verapamil Hydrochloride Injection

ベラパミル塩酸塩注射液

Verapamil Hydrochloride Injection is an aqueous injection.

It contains not less than 93.0% and not more than 107.0% of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4$.HCl: 491.06).

Method of preparation Prepare as directed under Injections, with Verapamil Hydrochloride.

Description Verapamil Hydrochloride Injection is a clear, colorless liquid.

Identification To 1 mL of the sample solution obtained in the Assay, add 0.02 mol/L hydrochloric acid TS to make 50 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits maxima between 227 nm and 231 nm, and between 276 nm and 280 nm.

pH Being specified separately when the drug is granted approval based on the Law.

Bacterial endotoxins <*4.01*> Less than 12 EU/mg.

Extractable volume <*6.05*> It meets the requirement.

Foreign insoluble matter <*6.06*> Perform the test according to Method 1: it meets the requirement.

Insoluble particulate matter <*6.07*> It meets the requirement.

Sterility ⟨*4.06*⟩ Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Pipet a volume of Verapamil Hydrochloride Injection, equivalent to about 10 mg of verapamil hydrochloride ($C_{27}H_{38}N_2O_4$.HCl), add 0.02 mol/L hydrochloric acid TS to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 50 mg of verapamil hydrochloride for assay, previously dried at 105°C for 2 hours, dissolve in 0.02 mol/L hydrochloric acid TS to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions, and determine the peak areas, A_T and A_S, of verapamil in each solution.

Amount (mg) of verapamil hydrochloride ($C_{27}H_{38}N_2O_4$.HCl)
$= M_S \times A_T/A_S \times 1/5$

M_S: Amount (mg) of verapamil hydrochloride for assay taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 279 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of methanol, water and perchloric acid (550:450:1).

Flow rate: Adjust so that the retention time of verapamil is about 5 minutes.

System Suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of verapamil are not less than 2000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of verapamil is not more than 1.0%.

Containers and storage Containers—Hermetic containers, and colored containers may be used.

Storage—Light-resistant.

Delete the following Monograph:

Compound Vitamin B Powder

複方ビタミン B 散

Crude Drugs and Related Drugs

Amomum Seed

シュクシャ

Change the Origin/limits of content as follows:

Amomum Seed is the seed mass of *Amomum villosum* Loureiro var. *xanthioides* T. L. Wu & S. J. Chen, *Amomum villosum* Loureiro var. *villosum* or *Amomum longiligulare* T. L. Wu (*Zingiberaceae*).

Artemisia Capillaris Flower

インチンコウ

Change the Description as follows:

Description Capitulum, of ovoid to spherical, about 1.5 – 2 mm in length, about 2 mm in diameter, with linear leaves and pedicels. Outer surface of capitulum, light green to light yellow-brown in color; outer surface of leaf, green to green-brown; outer surface of pedicel, green-brown to dark brown. Under a magnifying glass, at the capitulum, involucral scale in 3 – 4 succubous rows; outer scale, of ovate with obtuse; inner scale, of elliptical, 1.5 mm in length, longer than outer one, with keel midrib and thin membranous margin. Floret, tubular; marginal flower, of female; disk flower, of hermaphrodite. Achene, of obovoid, 0.8 mm in length. Light in texture.

Odor, characteristic, slight; taste, slightly acrid, which gives slightly numbing sensation to the tongue.

Belladonna Root

ベラドンナコン

Change the Description as follows:

Description Cylindrical root, usually 10 – 30 cm in length, 0.5 – 4 cm in diameter; often cut crosswise or lengthwise; externally grayish brown to grayish yellow-brown, with longitudinal wrinkles; periderm often removed; fractured surface is light yellow to light yellow-brown in color and is powdery.

Almost odorless.

Bitter Tincture

苦味チンキ

Change the Identification (2) as follows:

Identification

(2) Use Bitter Tincture as the sample solution. Separately, to 0.5 g of pulverized Bitter Orange Peel add 10 mL of methanol, shake for 5 minutes, filter, and use the filtrate as the standard solution (1). Proceed with 0.5 g each of pulverized Swertia Herb and Japanese Zanthoxylum Peel in the same manner, and use the solutions so obtained as the standard solution (2) and the standard solution (3). Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL of the sample solution and 5 μL each of standard solutions (1), (2) and (3) on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, ethanol (99.5) and water (8:2:1) to a distance of about 7 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm): one of the several spots obtained from the sample solution has the same *R*f value with the clear spot at an *R*f value of about 0.7 from the standard solution (3). Spray evenly vanillin-sulfuric acid-ethanol TS for spraying on the plate, and heat the plate at 105°C for 5 minutes: two of the several spots from the sample solution show the same color tone and *R*f with the clear spot at an *R*f value of about 0.4 from the standard solution (1), and the clear spot at an *R*f value of about 0.35 from the standard solution (2).

Bofutsushosan Extract

防風通聖散エキス

Change the Identification (1) as follows:

Identification (1) To 2.0 g of the dry extract (or 6.0 g of the viscous extract) add 10 mL of water, shake, then add 10 mL of diethyl ether, shake, and centrifuge. Separate the diethyl ether layer, add 10 mL of sodium hydroxide TS, shake, centrifuge, separate the diethyl ether layer, and use this solution as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 20 μL of the sample solution and 10 μL of the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of butyl acetate and hexane (2:1) to a distance of about 7 cm, and air-dry the plate. Examine

under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Japanese Angelica Root; Cnidium Rhizome).

Boiogito Extract

防已黄耆湯エキス

Change the Assay (1) as follows:

Assay (1) Sinomenine—Weigh accurately about 0.5 g of the dry extract (or an amount of the viscous extract, equivalent to about 0.5 g of the dried substance), add 20 mL of diethyl ether, shake, then add 5.0 mL of 0.1 mol/L hydrochloric acid TS, and shake for 10 minutes, centrifuge, and remove the upper layer. Add 20 mL of diethyl ether, proceed in the same manner as described above, and remove the upper layer. To the aqueous layer add 5.0 mL of diluted sodium hydroxide TS (1 in 10) and 10 mL of methanol, shake for 15 minutes, centrifuge, and take the supernatant liquid. To the residue add 20 mL of diluted methanol (1 in 2), shake for 15 minutes, centrifuge, and take the supernatant liquid. Combine all the supernatant liquids, add diluted methanol (1 in 2) to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately about 5 mg of sinomenine for assay, dissolve in diluted methanol (1 in 2) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of sinomenine in each solution.

$$\text{Amount (mg) of sinomenine} = M_S \times A_T/A_S \times 1/2$$

M_S: Amount (mg) of sinomenine for assay taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30°C.

Mobile phase: To 3 g of sodium lauryl sulfate add 350 mL of acetonitrile, shake, then add 650 mL of water and 1 mL of phosphoric acid to dissolve lauryl sulfate.

Flow rate: 1.0 mL per minute (the retention time of sinomenine is about 18 minutes).

System suitability—

System performance: When the procedure is run with 10 μL each of the sample solution, the standard solution of sinomenine and the standard solution of glycyrrhizic acid obtained in Assay (2) under the above operating conditions, peaks of sinomenine and glycyrrhizic acid are observed in the sample solution, glycyrrhizic acid and sinomenine are eluted in this order with the resolution between these peaks being not less than 4.5. Furthermore, except for the peak of glycyrrhizic acid, distinct peaks are observed before and after the peak of sinomenine, and the resolutions between sinomenine and these peaks are respectively not less than 1.5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sinomenine is not more than 1.5%.

Calumba

コロンボ

Change the Purity (1) as follows:

Purity (1) Heavy metals <*1.07*>—Proceed with 2.0 g of pulverized Calumba according to Method 3, and perform the test. Prepare the control solution with 3.0 mL of Standard Lead Solution (not more than 15 ppm).

Powdered Calumba

コロンボ末

Change the Purity (1) as follows:

Purity (1) Heavy metals <*1.07*>—Proceed with 2.0 g of Powdered Calumba according to Method 3, and perform the test. Prepare the control solution with 3.0 mL of Standard Lead Solution (not more than 15 ppm).

Cassia Seed

ケツメイシ

Change the Identification as follows:

Identification To 1.0 g of pulverized Cassia Seed add 10 mL of diluted methanol (4 in 5), heat on a water bath for 5 minutes, and filter. Evaporate the solvent of the filtrate, dissolve the residue in 5 mL of water, add 2 mL of ethyl acetate, and shake for 10 minutes. Centrifuge this solution, and use the upper layer as the sample solution. Perform the test with the sample solution as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL of the sample solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of diethyl ether, cyclohexane and formic acid (5:5:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly potassium hydroxide-ethanol TS on the plate: an orange to yellow-brown spot appears at an *R*f value of about 0.35.

Chrysanthemum Flower

キクカ

Change the Description as follows:

Description 1) *Chrysanthemum morifolium* origin—Capitulum, 15 – 40 mm in diameter; involucre, consisting of 3 to 4 rows of involucral scales, often with peduncle; the outer involucral scale, linear to lanceolate; inner involucral scale, narrow ovate to ovate; ligulate flowers, numerous, white to yellow in color; tubular flowers, small in number, light yellow-brown, occasionally degenerate; outer surface of involucre, green-brown to brown; light in texture and easy to break.

Odor, characteristic; taste, slightly bitter.

2) *Chrysanthemum indicum* origin—Capitulum, 3 – 10 mm in diameter; involucre, consisting of 3 to 5 rows of involucral scales, often with peduncle; the outer involucral scale, linear to lanceolate; inner involucral scale, narrow ovate to ovate; ligulate flower, in a single circle, yellow to light yellow-brown in color; tubular flowers, numerous, light yellow-brown; outer surface of involucre, yellow-brown to brown; light in texture and easy to break.

Odor, characteristic; taste, slightly bitter.

Eucalyptus Oil

ユーカリ油

Change the Assay as follows:

Assay Weigh accurately about 0.1 g each of Eucalyptus Oil and cineol for assay, and dissolve each in hexane to make exactly 25 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal standard solution to each, then add hexane to make 100 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 2 μL each of the sample solution and standard solution as directed under Gas Chromatography <*2.02*> according to the following conditions. Calculate the ratios, Q_T and Q_S, of the peak area of cineol to that of the internal standard.

$$\text{Amount (mg) of cineol } (C_{10}H_{18}O) = M_S \times Q_T/Q_S$$

M_S: Amount (mg) of cineol for assay taken

Internal standard solution—A solution of anisol in hexane (1 in 250).

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A glass column 3 mm in inside diameter and 5 m in length, packed with silanized porous silica gel for gas chromatography coated in 5% with alkylene glycol phthalate ester for gas chromatography (150 to 180 μm in particle diameter).

Column temperature: A constant temperature of about 120°C.

Carrier gas: Nitrogen.

Flow rate: Adjust so that the retention time of cineol is about 11 minutes.

System suitability—

System performance: Dissolve 0.1 g each of cineol for assay and limonene in 25 mL of hexane. To 1 mL of this solution add hexane to make 20 mL. When the procedure is run with 2 μL of this solution under the above operating conditions, limonene and cineol are eluted in this order with the resolution between these peaks being not less than 1.5.

System repeatability: When the test is repeated 6 times with 2 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of cineol to that of the internal standard is not more than 1.0%.

Gastrodia Tuber

テンマ

Change the origin/limits of content as follows:

Gastrodia Tuber is the tuber of *Gastrodia elata* Blume (*Orchidaceae*), after being passed through hot water or steamed.

Glycyrrhiza Extract

カンゾウエキス

Change the Method of preparation as follows:

Method of preparation

1) To 1 kg of fine cuttings of Glycyrrhiza or the root and stolon of *Glycyrrhiza glabra* Linné (*Leguminosae*) which meets the requirement of Glycyrrhiza add 5 L of Water, Purified Water or Purified Water in Containers, and macerate for 2 days. Filter the macerated solution through a cloth filter. Add 3 L of Water, Purified Water or Purified Water in Containers to the residue, macerate again for 12 hours, and filter through a cloth filter. Evaporate the combined filtrates until the whole volume becomes 3 L. After cooling, add 1 L of Ethanol, and allow to stand in a cold place for 2 days. Filter, and evaporate the filtrate to a viscous extract.

2) Take Glycyrrhiza or the root and stolon of *Glycyrrhiza glabra* Linné (*Leguminosae*) which meets the requirement of Glycyrrhiza, pulverized to suitable sizes, and prepare the viscous extract as directed under Extracts using Water, Purified Water or Purified Water in Containers as the solvent. Immediately before making a millet jelly-like consistency for the viscous extract, add Ethanol, Anhydrous Ethanol or ethanol (99.5) to the extract, allow it to stand in a cold place, filter, and concentrate the filtrate to prepare.

Crude Glycyrrhiza Extract

カンゾウ粗エキス

Change the Method of preparation as follows:

Method of preparation Take Glycyrrhiza or the root and stolon of *Glycyrrhiza glabra* Linné (*Leguminosae*) which meets the requirement of Glycyrrhiza, pulverized to suitable sizes, and prepare the dry extracts as directed under Extracts using Water, Purified Water or Purified Water in Containers as the solvent.

Add the following:

Goshuyuto Extract

呉茱萸湯エキス

Goshuyuto Extract contains not less than 0.3 mg (for preparation prescribed 3 g of Euodia Fruit) or not less than 0.4 mg (for preparation prescribed 4 g of Euodia Fruit) of evodiamine, and not less than 0.5 mg and not more than 2.0 mg (for preparation prescribed 1 g of Ginger) or not less than 0.7 mg and not more than 2.8 mg (for preparation prescribed 1.5 g of Ginger) of [6]-gingerol, per extract prepared with the amount specified in the Method of preparation.

Method of preparation

	1)	2)	3)
Euodia Fruit	3 g	4 g	3 g
Ginger	1 g	1.5 g	1.5 g
Ginseng	2 g	3 g	2 g
Jujube	4 g	3 g	4 g

Prepare a dry extract or viscous extract as directed under Extracts, according to the prescription 1) to 3), using the crude drugs shown above.

Description Goshuyuto Extract occurs as a light brown to light red-yellow powder, or a black-brown viscous extract. It has a slight odor and a hot and bitter taste.

Identification (1) To 1.0 g of the dry extract (or 3.0 g of the viscous extract) add 10 mL of sodium hydroxide TS, shake, add 5 mL of 1-butanol, shake, centrifuge, and use the supernatant liquid as the sample solution. Separately, to 1 g of pulverized euodia fruit add 10 mL of methanol, shake, centrifuge, and use the supernatant liquid as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 1 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of acetone, 2-propanol, water and formic acid (7:7:1:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot (*R*f value: about 0.5) from the standard solution (Euodia Fruit).

(2) To 1.0 g of the dry extract (or 3.0 g of the viscous extract) add 10 mL of water, shake, add 25 mL of diethyl ether, and shake. Separate the diethyl ether layer, evaporate the solvent under reduced pressure, add 2 mL of diethyl ether to the residue, and use this solution as the sample solution. Separately, dissolve 1 mg of [6]-gingerol for thin-layer chromatography in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL of the sample solution and 5 μL of the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and hexane (1:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly 4-dimethylaminobenzaldehyde TS for spraying on the plate, heat the plate at 105°C for 5 minutes, allow to cool, and spray water: one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-green to grayish green spot from the standard solution (Ginger).

(3) To 1.0 g of the dry extract (or 3.0 g of the viscous extract) add 10 mL of sodium hydroxide TS, shake, add 5 mL of 1-butanol, shake, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 1 mg of ginsenoside Rb_1 for thin-layer chromatography in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, 1-propanol, water and acetic acid (100) (7:5:4:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly vanillin-sulfuric acid-ethanol TS for spraying on the plate, heat the plate at 105°C for 5 minutes, and allow to cool: one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-purple spot from the standard solution (Ginseng).

Purity (1) Heavy metals <*1.07*>—Prepare the test solution with 1.0 g of the dry extract (or an amount of the viscous extract, equivalent to 1.0 g of the dried substance) as directed under Extracts (4), and perform the test (not more than 30 ppm).

(2) Arsenic <*1.11*>—Prepare the test solution with 0.67 g of the dry extract (or an amount of the viscous extract, equivalent to 0.67 g of the dried substance) according to Method 3, and perform the test (not more than 3 ppm).

Loss on drying <*2.41*> The dry extract: Not more than 11.0% (1 g, 105°C, 5 hours).

The viscous extract: Not more than 66.7% (1 g, 105°C, 5 hours).

Total ash <*5.01*> Not more than 10.0%, calculated on the dried basis.

Assay (1) Evodiamine—Weigh accurately about 0.5 g of the dry extract (or an amount of the viscous extract, equivalent to about 0.5 g of the dried substance), add exactly 50 mL of diluted methanol (7 in 10), shake for 30 minutes, filter, and use the filtrate as the sample solution. Separately, weigh accurately about 10 mg of evodiamine for assay, and dissolve in methanol to make exactly 200 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of evodiamine in each solution.

$$\text{Amount (mg) of evodiamine} = M_S \times A_T/A_S \times 1/4$$

M_S: Amount (mg) of evodiamine for assay taken, calculated on the basis of the content obtained by qNMR

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 282 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of water, acetonitrile and phosphoric acid (620:380:1).

Flow rate: 1.0 mL per minute (the retention time of evodiamine is about 18 minutes).

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of evodiamine are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of evodiamine is not more than 1.5%.

(2) [6]-Gingerol—Weigh accurately about 0.5 g of the dry extract (or an amount of the viscous extract, equivalent to about 0.5 g of the dried substance), add exactly 50 mL of diluted methanol (7 in 10), shake for 30 minutes, filter, and use the filtrate as the sample solution. Separately, weigh accurately about 10 mg of [6]-gingerol for assay, dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of [6]-gingerol in each solution.

$$\text{Amount (mg) of [6]-gingerol} = M_S \times A_T/A_S \times 1/20$$

M_S: Amount (mg) of [6]-gingerol for assay taken

Operating conditions—

Detector, column, column temperature and mobile phase: Proceed as directed in the operating conditions in (1).

Flow rate: 1.0 mL per minute (the retention time of [6]-gingerol is about 14 minutes).

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of [6]-gingerol are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of [6]-gingerol is not more than 1.5%.

Containers and storage Containers—Tight containers.

Hochuekkito Extract

補中益気湯エキス

Change the Identification (5) as follows:

Identification

(5) To 3.0 g of the dry extract (or 9.0 g of the viscous extract) add 30 mL of water, shake, then add 50 mL of diethyl ether, shake, and separate the diethyl ether layer. Evaporate the layer under reduced pressure, add 1 mL of diethyl ether to the residue, and use this solution as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and hexane (1:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Japanese Angelica Root).

Japanese Angelica Root

トウキ

Add the following next to the Description as follows:

Identification To 1.0 g of pulverized Japanese Angelica Root add 5 mL of methanol, shake for 10 minutes, centrifuge, and use the supernatant liquid as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution (1). Dissolve 1 mg of scopoletin for thin-layer chromatography in 10 mL of methanol, and use this solution as the standard solution (2). Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL of the sam-

ple solution and 5 μL each of the standard solutions (1) and (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of hexane, acetone and acetic acid (100) (30:25:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): two of the several spots obtained from the sample solution have the same color tones and *R*f values with the corresponding blue-white fluorescent spots from the standard solutions (1) and (2).

Powdered Japanese Angelica Root

トウキ末

Add the following next to the Description as follows:

Identification To 1.0 g of Powdered Japanese Angelica Root add 5 mL of methanol, shake for 10 minutes, centrifuge, and use the supernatant liquid as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution (1). Dissolve 1 mg of scopoletin for thin-layer chromatography in 10 mL of methanol, and use this solution as the standard solution (2). Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL of the sample solution and 5 μL each of the standard solutions (1) and (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of hexane, acetone and acetic acid (100) (30:25:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): two of the several spots obtained from the sample solution have the same color tones and *R*f values with the corresponding blue-white fluorescent spots from the standard solutions (1) and (2).

Juzentaihoto Extract

十全大補湯エキス

Change the Identification (5) as follows:

Identification

(5) Shake 1.0 g of the dry extract (or 3.0 g of the viscous extract) with 15 mL of water and 5 mL of 0.1 mol/L hydrochloric acid TS, add 25 mL of diethyl ether, and shake. Separate the diethyl ether layer, evaporate the layer under reduced pressure, then add 2 mL of diethyl ether to the residue, and use this solution as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and hexane (1:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Cnidium Rhizome; Japanese Angelica Root).

Kakkontokasenkyushin'i Extract

葛根湯加川芎辛夷エキス

Change the Identification (7) as follows:

Identification

(7) Shake 1.0 g of the dry extract (or 3.0 g of the viscous extract) with 15 mL of water and 5 mL of 0.1 mol/L hydrochloric acid TS, and then shake with 25 mL of diethyl ether. Separate the diethyl ether layer, evaporate the solvent under reduced pressure, then dissolve the residue in 2 mL of diethyl ether, and use this solution as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and hexane (1:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Cnidium Rhizome).

Kamikihito Extract

加味帰脾湯エキス

Change the Identification (5) as follows:

Identification

(5) To 3.0 g of the dry extract (or 9.0 g of the viscous ex tract) add 15 mL of water, shake, then add 25 mL of diethyl ether, and shake. Separate the diethyl ether layer, evaporate the solvent under reduced pressure, then add 2 mL of diethyl ether to the residue, and use the solution as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL of the sample solution and 2 μL of the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of butyl acetate and hexane (2:1) to a distance of about 7 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Japanese Angelica Root).

Kamishoyosan Extract

加味逍遙散エキス

Change the Identification (1) as follows:

Identification (1) To 2.0 g of the dry extract (or 6.0 g of the viscous extract) add 10 mL of water, shake, then add 5 mL of diethyl ether, shake, centrifuge, and use the diethyl ether layer as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and hexane (1:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Japanese Angelica Root).

Lithospermum Root

シコン

Change the Purity (1) as follows:

Purity (1) Heavy metals <*1.07*>—Proceed with 2.0 g of pulverized Lithospermum Root according to Method 3, and perform the test. Prepare the control solution with 3.0 mL of Standard Lead Solution (not more than 15 ppm).

Lycium Bark

ジコッピ

Change the Purity (1) as follows:

Purity (1) Heavy metals <*1.07*>—Proceed with 2.0 g of pulverized Lycium Bark according to Method 3, and perform the test. Prepare the control solution with 3.0 mL of Standard Lead Solution (not more than 15 ppm).

Nux Vomica

ホミカ

Change the Description as follows:

Description Disk, often slightly bent, 1 – 3 cm in diameter, 0.3 – 0.5 cm in thickness; externally light grayish yellow-green to light grayish brown, covered densely with lustrous appressed hairs radiating from the center to the circumference; on both sides, the margin and the central part bulged a little; the dot-like micropyle situated at one point on the margin, and from which usually a raised line runs to the center on one side; extremely hard in texture; when cracked upon soaking in water, the seed coat thin, the interior consisting of two horny, light grayish yellow endosperms, and leaving a central narrow cavity at the center; a white embryo, about 0.7 cm in length, situated at one end between the inner surfaces of the endosperms.

Odorless.

Oriental Bezoar

ゴオウ

Change the origin/limits of content:

Oriental Bezoar is a stone formed in the gall sac of *Bos taurus* Linné var. *domesticus* Gmelin (*Bovidae*).

It contains not less than 10.0% of bilirubin.

Delete the Identification (2):

Add the following next to the Total ash:

Assay Conduct this procedure without exposure to light using light-resistant vessels. The following sample solution and standard solution should be prepared before use. Weigh accurately about 10 mg of pulverized Oriental Bezoar, add 10 mL of a mixture of dimethyl sulfoxide and acetic acid (100) (9:1), warm at 60°C for 20 minutes, and add a mixture of dimethyl sulfoxide and acetic acid (100) (9:1) to make exactly 50 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, filter through a membrane filter, and use the filtrate as the sample solution. Separately, weigh accurately about 10 mg of bilirubin for assay, add about 350 mg of L-ascorbic acid, and dissolve in a mixture of dimethyl sulfoxide and acetic acid (100) (9:1) to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of bilirubin in each solution.

$$\text{Amount (mg) of bilirubin} = M_S \times A_T/A_S \times 1/2$$

M_S: Amount (mg) of bilirubin for assay taken

Operating conditions—

Detector: A visible absorption photometer (wavelength: 450 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30°C.

Mobile phase: A mixture of acetonitrile and diluted acetic

acid (100) (1 in 100) (19:1).

Flow rate: Adjust so that the retention time of bilirubin is about 10 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of bilirubin are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of bilirubin is not more than 1.5%.

Delete the Content of the active principle:

Otsujito Extract

乙字湯エキス

Change the Identification (1) as follows:

Identification **(1)** Shake 2.0 g of the dry extract (or 6.0 g of the viscous extract) with 10 mL of water, add 10 mL of diethyl ether, shake, and centrifuge. Separate the diethyl ether layer, add 10 mL of sodium hydroxide TS, shake, centrifuge, separate the diethyl ether layer, and use this layer as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of butyl acetate and hexane (2:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Japanese Angelica Root).

Platycodon Root

キキョウ

Delete the Identification (1), move up (2) to (1) and add the following next to (1):

Identification

(2) To 2.0 g of pulverized Platycodon Root add 20 mL of sodium carbonate TS, and shake. Add 5 mL of 1-butanol, shake for 10 minutes, centrifuge, and use the 1-butanol layer as the sample solution. Separately, dissolve 1 mg of platycodin D for thin-layer chromatography in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of 1-propanol, ethyl acetate, water and acetic acid (100) (5:3:2:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat the plate at 105°C for 5 minutes: one of the several spots obtained from the sample solution and a spot from the standard solution show the same color tone and the same *R*f value.

Powdered Platycodon Root

キキョウ末

Delete the Identification (1), move up (2) to (1) and add the following next to (1):

Identification

(2) To 2.0 g of Powdered Platycodon Root add 20 mL of sodium carbonate TS, and shake. Add 5 mL of 1-butanol, shake for 10 minutes, centrifuge, and use the 1-butanol layer as the sample solution. Separately, dissolve 1 mg of platycodin D for thin-layer chromatography in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of 1-propanol, ethyl acetate, water and acetic acid (100) (5:3:2:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat the plate at 105°C for 5 minutes: one of the several spots obtained from the sample solution and a spot from the standard solution show the same color tone and the same *R*f value.

Platycodon Fluidextract

キキョウ流エキス

Change the Method of preparation and Identification as follows:

Method of preparation **1)** Take coarse powder of Platycodon Root, and prepare the fluidextract as directed under Fluidextracts using 25 vol% ethanol. An appropriate quantity of Ethanol and Purified Water or Purified Water in Containers may be used in place of 25 vol% ethanol.

2) Take Platycodon Root pulverized to suitable sizes, and prepare the fluidextract as directed under Fluidextracts using 25 vol% ethanol or diluted ethanol (1 in 4) as the solvent.

Identification To 2 mL of Platycodon Fluidextract add 20 mL of water and 5 mL of 1-butanol, mix, shake for 10 minutes, centrifuge, and use the 1-butanol layer as the sample solution. Separately, dissolve 1 mg of platycodin D for thin-layer chromatography in 1 mL of methanol, and use

this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of 1-propanol, ethyl acetate, water and acetic acid (100) (5:3:2:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat the plate at 105°C for 5 minutes: one of the several spots obtained from the sample solution has the same color tone and *R*f value with the spot from the standard solution.

Add the following next to the Identification:

Alcohol number <*1.01*> Apply to Platycodon Fluidextract prepared by the Method of preparation 2). 2.0 – 3.0 (Method 1).

Change the Content of the active principle as follows:

Content of the active principle Transfer exactly 5 mL of Platycodon Fluidextract to a tared beaker or porcelain dish, evaporate to dryness on a water bath, and dry at 105°C for 5 hours: the mass of the residue is not less than 0.50 g.

Polygala Root

オンジ

Change the Identification (2) as follows:

Identification

(2) To 1.0 g of pulverized Polygala Root add 10 mL of a solution of sodium hydroxide (1 in 10), and heat under a reflux condenser on a water bath for 20 minutes. After cooling, add 10 mL of dilute hydrochloric acid, and shake. After cooling, add 10 mL of 1-butanol, shake for 10 minutes, centrifuge, and use the upper layer as the sample solution. Perform the test with the sample solution as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL of the sample solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol, water and acetic acid (100) (20:4:2:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat the plate at 105°C for 10 minutes: a red-brown to light brown spot appears at an *R*f value of about 0.35.

Powdered Polygala Root

オンジ末

Change the Identification (2) as follows:

Identification

(2) To 1.0 g of Powdered Polygala Root add 10 mL of a solution of sodium hydroxide (1 in 10), and heat under a reflux condenser on a water bath for 20 minutes. After cooling, add 10 mL of dilute hydrochloric acid, and shake. After cooling, add 10 mL of 1-butanol, shake for 10 minutes, centrifuge, and use the upper layer as the sample solution. Perform the test with the sample solution as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL of the sample solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol, water and acetic acid (100) (20:4:2:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat the plate at 105°C for 10 minutes: a red-brown to light brown spot appears at an *R*f value of about 0.35.

Safflower

コウカ

Change the Identification as follows:

Identification To 1.0 g of pulverized Safflower add 10 mL of a mixture of acetone and water (4:1), shake for 10 minutes, filter, and use the filtrate as the sample solution. Perform the test with the sample solution as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL of the sample solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, water, formic acid and methanol (35:15:10:2) to a distance of about 7 cm, and air-dry the plate: a red spot appears at an *R*f value of about 0.5.

Saposhnikovia Root and Rhizome

ボウフウ

Change the Purity (1) as follows:

Purity (1) Heavy metals <*1.07*>—Proceed with 2.0 g of pulverized Saposhnikovia Root and Rhizome according to Method 3, and perform the test. Prepare the control solution with 3.0 mL of Standard Lead Solution (not more than 15 ppm).

Add the following next to the Purity (3):

Purity

(4) Peucedanum ledebourielloides—Place 1.0 g of pulverized Saposhnikovia Root and Rhizome in a glass-stoppered centrifuge tube, add 5 mL of hexane, shake for 10 minutes, centrifuge, and use the supernatant liquid as the sample solution. Separately, place 1.0 g of peucedanum·ledebourielloides for purity in a glass-stoppered centrifuge tube, add 5 mL of hexane, shake for 10 minutes, centrifuge, and use the supernatant liquid as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for

thin-layer chromatography. Develop the plate with a mixture of hexane, ethyl acetate and acetic acid (100) (20:10:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): the sample solution shows no spot corresponding to the blue fluorescent spot at an *R*f value of about 0.4 obtained from the standard solution.

Scopolia Rhizome

ロートコン

Change the Description as follows:

Description Chiefly irregularly branched, slightly curved rhizome, about 15 cm in length, about 3 cm in diameter, occasionally longitudinally cut; externally grayish brown, with wrinkles; constrictions make the rhizome appear nodular; rarely, stem base at one end; stem scars at upper side of each node; roots or root scars on both sides and lower surface of rhizome; fractured surface granular, grayish white to light brown in color, with lighter colored cortex.

Odor characteristic.

Under a microscope <*5.01*>, xylem reveals groups of vessels arranged stepwise, and accompanied with xylem sieve tubes in medullary rays; parenchyma cells contain starch grains, and sometimes sand crystals of calcium oxalate.

Sinomenium Stem and Rhizome

ボウイ

Change the Identification as follows:

Identification To 1.0 g of pulverized Sinomenium Stem and Rhizome add 5 mL of methanol, shake for 10 minutes, filter, and use the filtrate as the sample solution. Separately, dissolve 1 mg of sinomenine for thin-layer chromatography in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 10 μL of the sample solution and 5 μL of the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl formate, 1-propanol, water and acetic acid (100) (3:3:2:2) to a distance of about 7 cm, and air-dry the plate. Spray evenly Dragendorff's TS for spraying on the plate, air-dry the plate, and spray evenly sodium nitrite TS on the plate: one of the several spots obtained from the sample solution and the spot from the standard solution show the same color tone and the same *R*f value. Further, a spot with the same color tone appears immediately below the spot.

Swertia Herb

センブリ

Change the Identification as follows:

Identification To 0.5 g of pulverized Swertia Herb add 10 mL of methanol, shake for 5 minutes, filter, and use the filtrate as the sample solution. Separately, dissolve 1 mg of Swertiamarin RS or swertiamarin for thin-layer chromatography in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, ethanol (99.5) and water (8:2:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly vanillin-sulfuric acid-ethanol TS for spraying on the plate, and heat the plate at 105°C for 5 minutes: one of the several spots obtained from the sample solution and the spot from the standard solution show the same color tone and *R*f value.

Powdered Swertia Herb

センブリ末

Change the Identification as follows:

Identification To 0.5 g of Powdered Swertia Herb add 10 mL of methanol, shake for 5 minutes, filter, and use the filtrate as the sample solution. Separately, dissolve 1 mg of Swertiamarin RS or swertiamarin for thin-layer chromatography in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, ethanol (99.5) and water (8:2:1) to a distance of about 7 cm, and air-dry the plate. Spray evenly vanillin-sulfuric acid-ethanol TS for spraying on the plate, and heat the plate at 105°C for 5 minutes: one of the several spots obtained from the sample solution and the spot from the standard solution show the same color tone and *R*f value.

Swertia and Sodium Bicarbonate Powder

センブリ·重曹散

Change the Identification (1) as follows:

Identification (1) To 10 g of Swertia and Sodium Bicarbonate Powder add 10 mL of ethanol (95), shake for 15 minutes, filter, and use the filtrate as the sample solution.

Separately, dissolve 2 mg of Swertiamarin RS or swertiamarin for thin-layer chromatography in 1 mL of ethanol (95), and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <2.03>. Spot 10 μL of the sample solution and 5 μL of the standard solution on a plate of silica gel for thin-layer chromatography. Proceed as directed in the Identification under Powdered Swertia Herb.

Toad Cake

センソ

Change the Description as follows:

Description A round disk with slightly dented bottom and protuberant surface, about 8 cm in diameter, about 1.5 cm in thickness, the mass of one disk being about 80 to 90 g; or a round disk with almost flattened surfaces on both sides, about 3 cm in diameter, and about 0.5 cm in thickness, the mass of one disk being about 8 g; externally red-brown to black-brown, somewhat lustrous, approximately uniform and horny, hard in texture, and difficult to break; fractured surface nearly flat, and edges of broken pieces red-brown and translucent.

Odorless.

Tokishakuyakusan Extract

当帰芍薬散エキス

Change the Identification (1) as follows:

Identification (1) Shake 1.0 g of the dry extract (or 3.0 g of the viscous extract) with 15 mL of water and 5 mL of 0.1 mol/L hydrochloric acid TS, then add 25 mL of diethyl ether, and shake. Separate the diethyl ether layer, evaporate the layer under reduced pressure, add 2 mL of diethyl ether to the residue, and use this solution as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <2.03>. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography, develop the plate with a mixture of ethyl acetate and hexane (1:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Japanese Angelica Root; Cnidium Rhizome).

Change the Assay (1) as follows:

Assay (1) (*E*)-Ferulic acid—Conduct this procedure without exposure to light, using light-resistant vessels. Weigh accurately about 0.5 g of the dry extract (or an amount of the viscous extract, equivalent to about 0.5 g of the dried substance), add exactly 50 mL of diluted methanol (1 in 2), shake for 15 minutes, filter, and use the filtrate as the sample solution. Separately, weigh accurately about 10 mg of (*E*)-ferulic acid for assay, and dissolve in diluted methanol (1 in 2) to make exactly 100 mL. Pipet 2 mL of this solution, add diluted methanol (1 in 2) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of (*E*)-ferulic acid in each solution.

$$\text{Amount (mg) of (}E\text{)-ferulic acid} = M_S \times A_T/A_S \times 1/50$$

M_S: Amount (mg) of (*E*)-ferulic acid for assay taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 320 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: Dissolve 7.8 g of sodium dihydrogen phosphate in 1000 mL of water, and add 2 mL of phosphoric acid. To 850 mL of this solution add 150 mL of acetonitrile.

Flow rate: 1.0 mL per minute [the retention time of (*E*)-ferulic acid is about 10 minutes].

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of (*E*)-ferulic acid are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of (*E*)-ferulic acid is not more than 1.5%.

Yokukansan Extract

抑肝散エキス

Change the Identification (1) as follows:

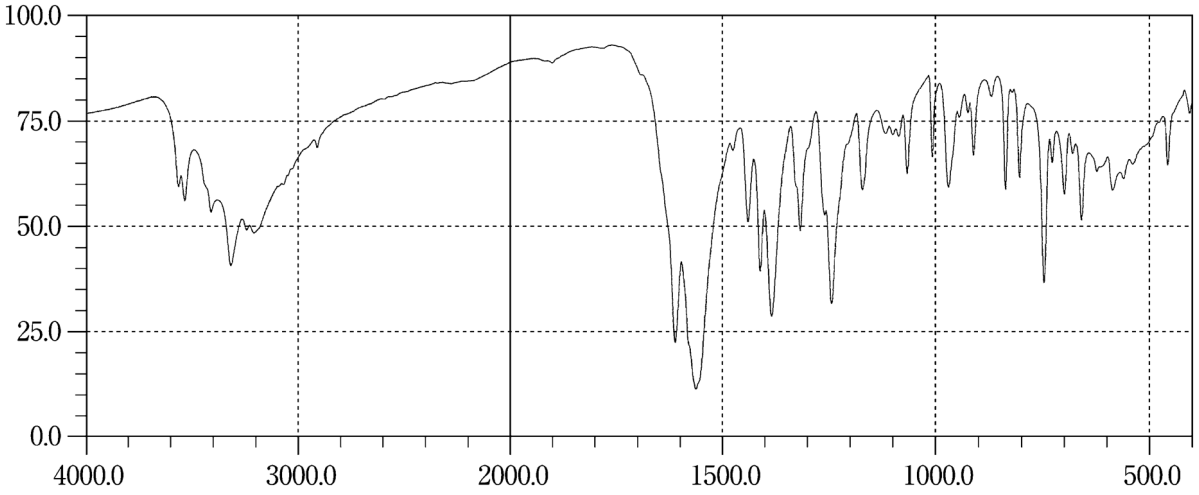
Identification (1) To 2.0 g of the dry extract (or 6.0 g of the viscous extract) add 10 mL of water, shake, then add 10 mL of diethyl ether, shake, and centrifuge. Separate the diethyl ether layer, add 10 mL of sodium hydroxide TS, shake, centrifuge, separate the diethyl ether layer, and use this layer as the sample solution. Separately, use (*Z*)-ligustilide TS for thin-layer chromatography as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <2.03>. Spot 10 μL each of the sample solution and standard solution on a plate of

silica gel for thin-layer chromatography. Develop the plate with a mixture of butyl acetate and hexane (2:1) to a distance of about 7 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 365 nm): one of the several spots obtained from the sample solution has the same color tone and *R*f value with the blue-white fluorescent spot from the standard solution (Japanese Angelica Root; Cnidium Rhizome).

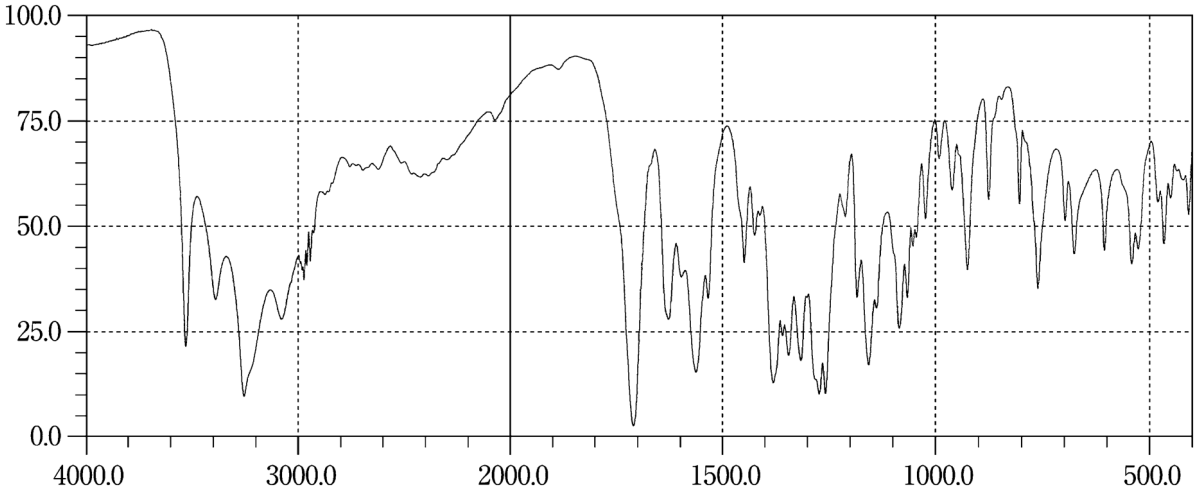
Infrared
Reference Spectra

Add the following spectra:

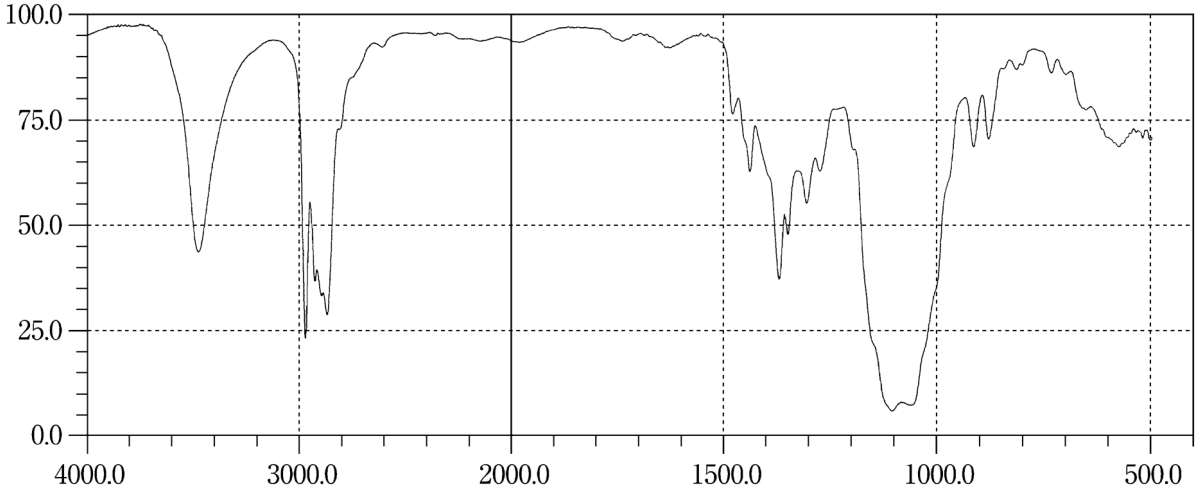
Bromfenac Sodium Hydrate



Doripenem Hydrate

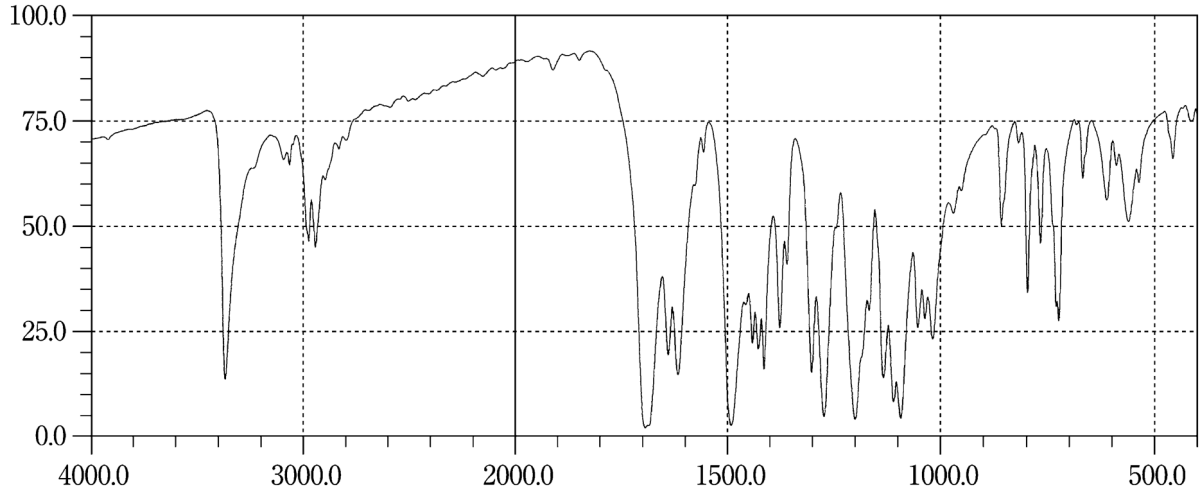


Ethylcellulose

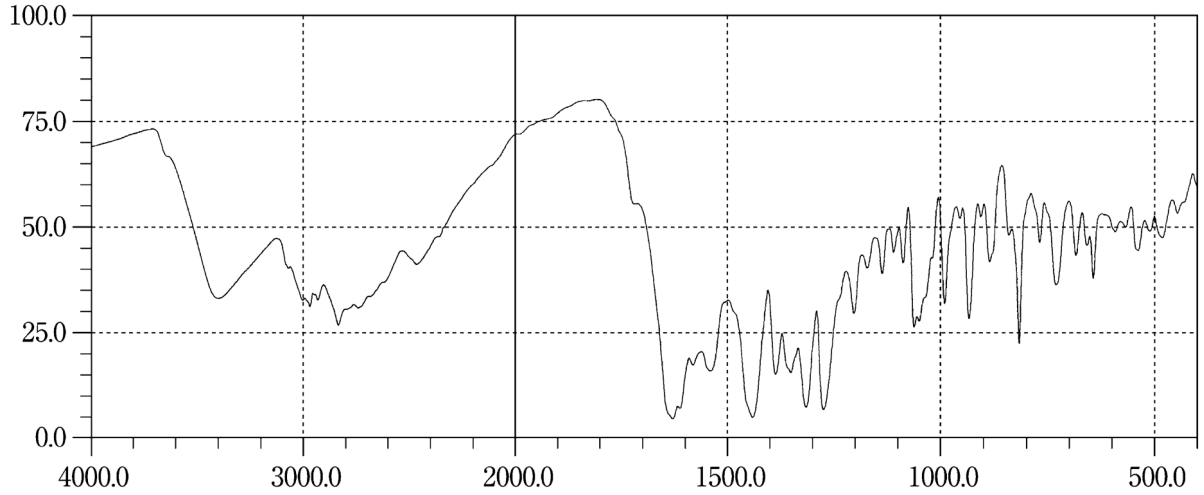


The JP Drugs are to be tested according to the provisions given in the pertinent monographs, General Notices, General Rules for Crude Drugs, General Rules for Preparations, and General Tests for their conformity to the Japanese Pharmacopoeia. (*See the General Notices 5.*)

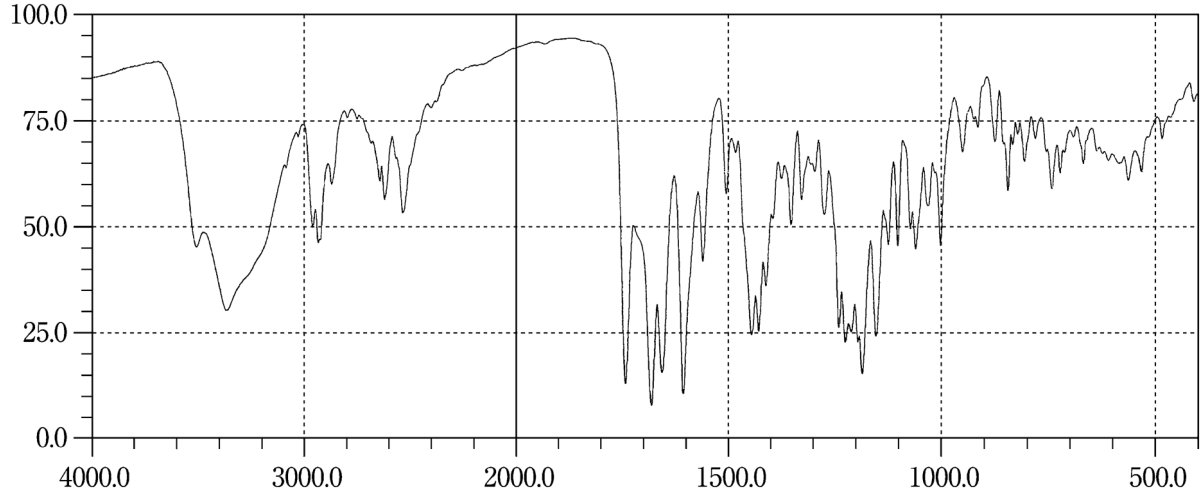
Felodipine



Gatifloxacin Hydrate

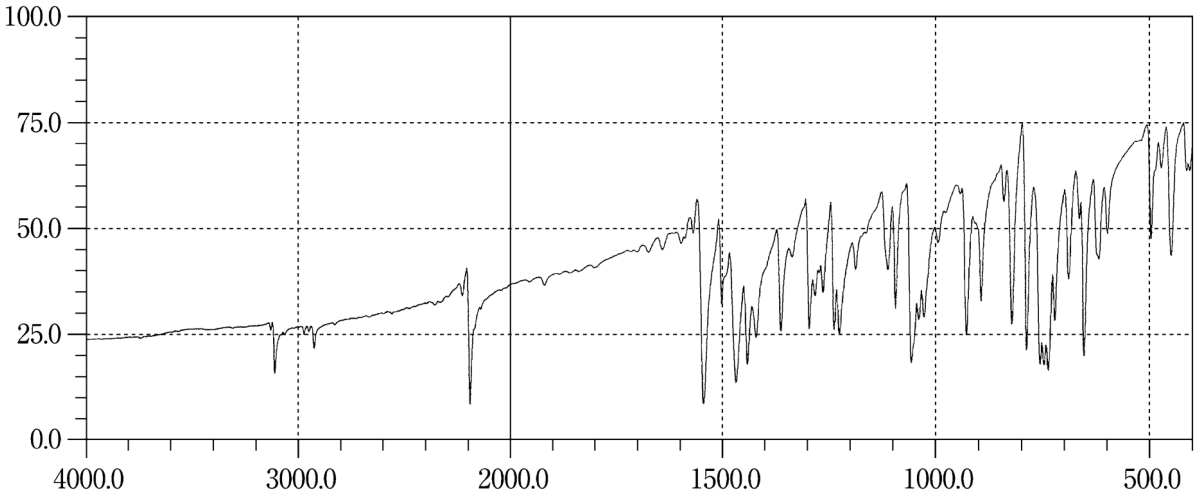


Irinotecan Hydrochloride Hydrate

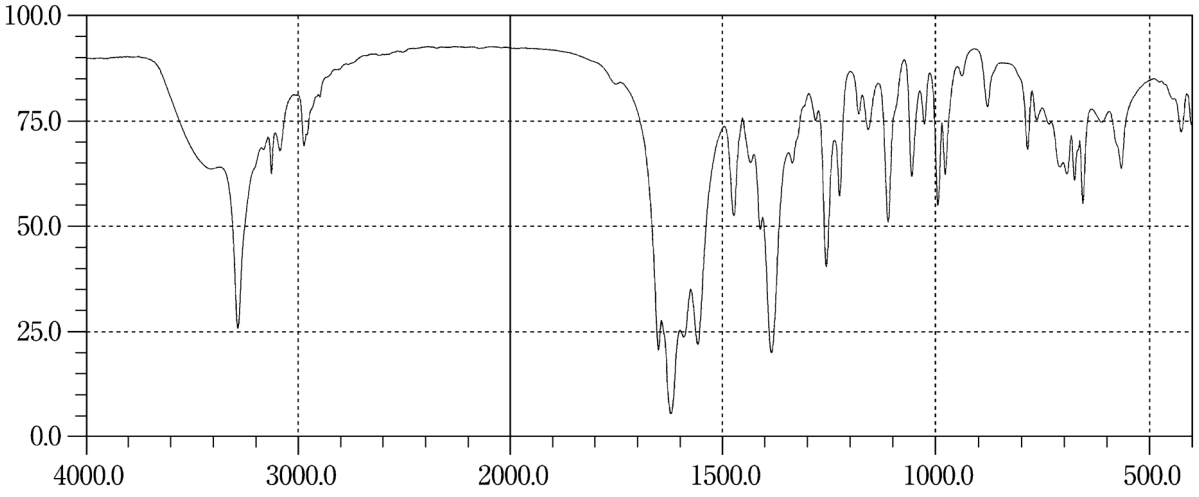


The JP Drugs are to be tested according to the provisions given in the pertinent monographs, General Notices, General Rules for Crude Drugs, General Rules for Preparations, and General Tests for their conformity to the Japanese Pharmacopoeia. (*See the General Notices 5.*)

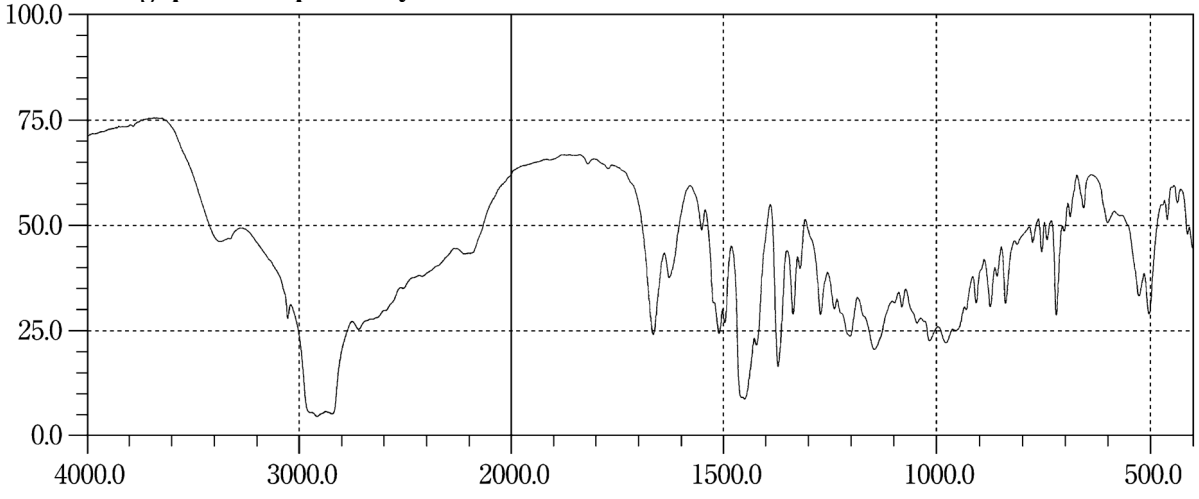
Lanoconazole



Polaprezinc



Sitagliptin Phosphate Hydrate



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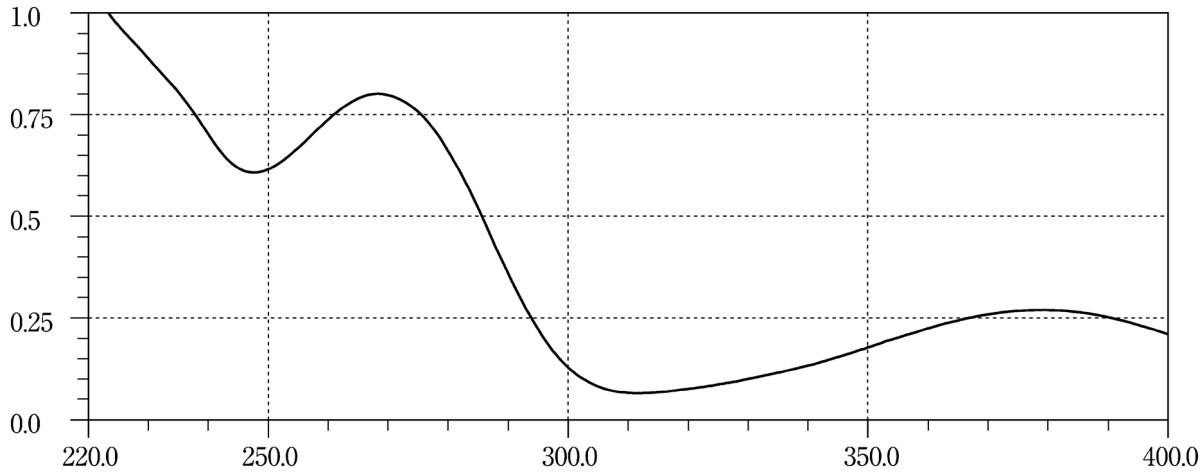
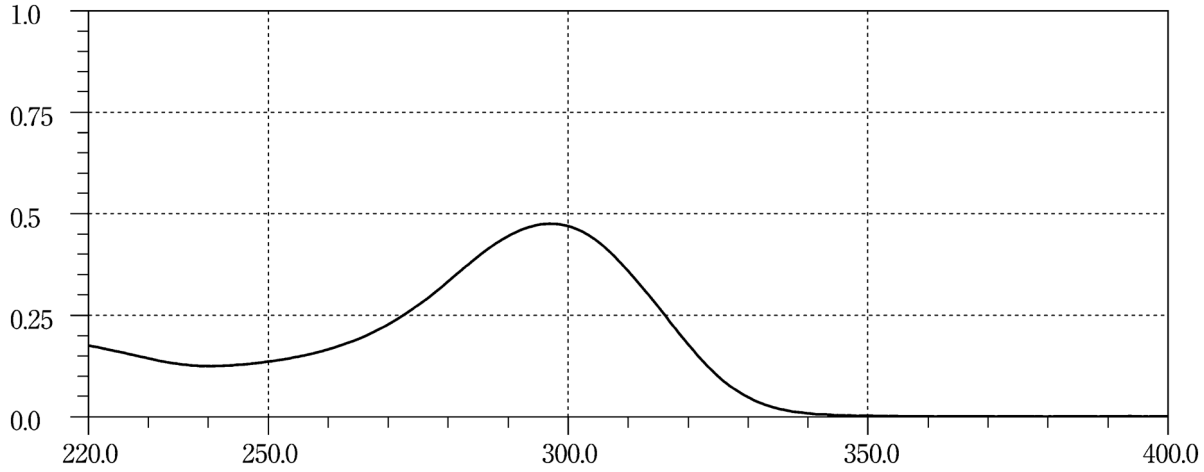
Ultraviolet-visible Reference Spectra

Add the following spectra:

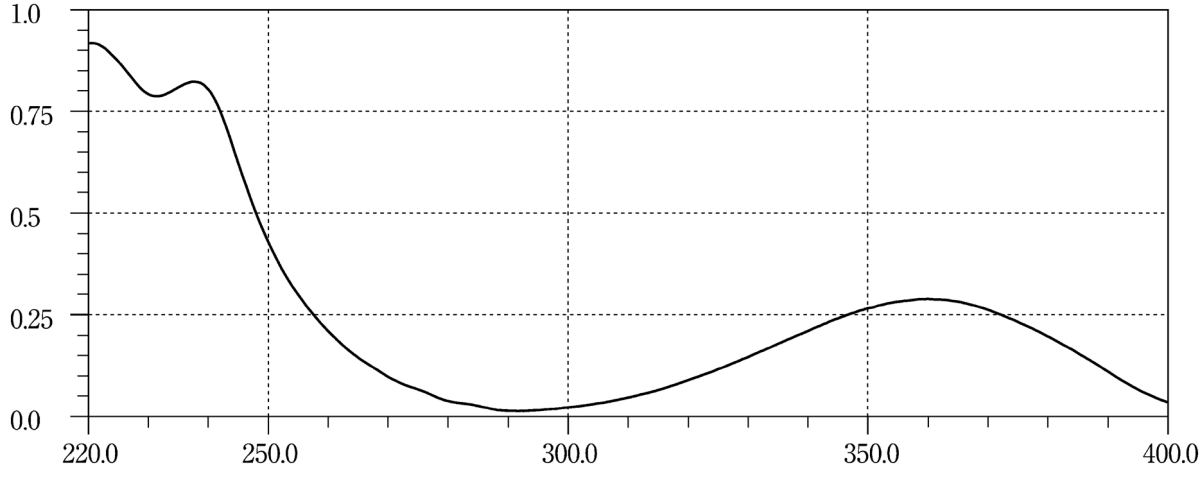
Bromfenac Sodium Hydrate



Doripenem Hydrate

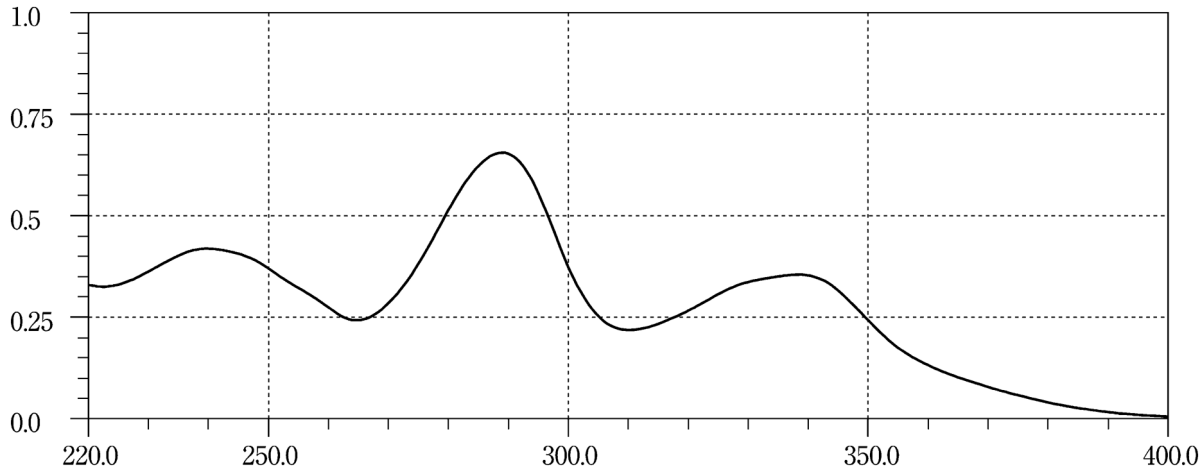


Felodipine

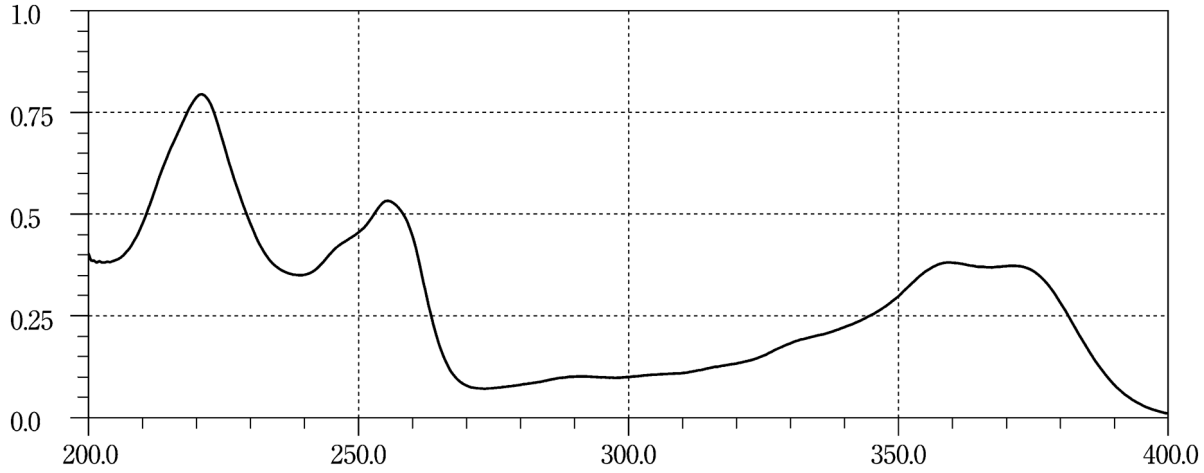


The JP Drugs are to be tested according to the provisions given in the pertinent monographs, General Notices, General Rules for Crude Drugs, General Rules for Preparations, and General Tests for their conformity to the Japanese Pharmacopoeia. (*See the General Notices 5.*)

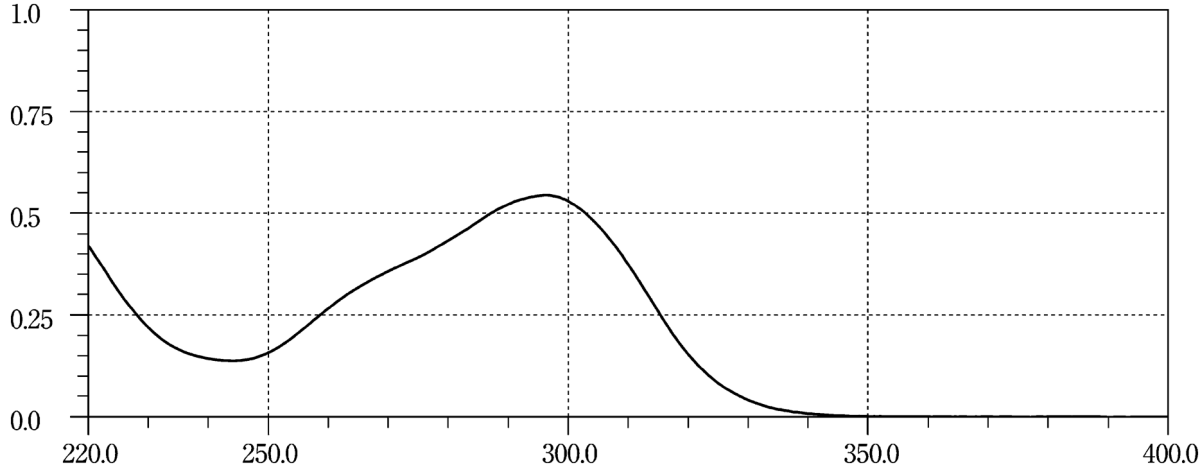
Gatifloxacin Hydrate



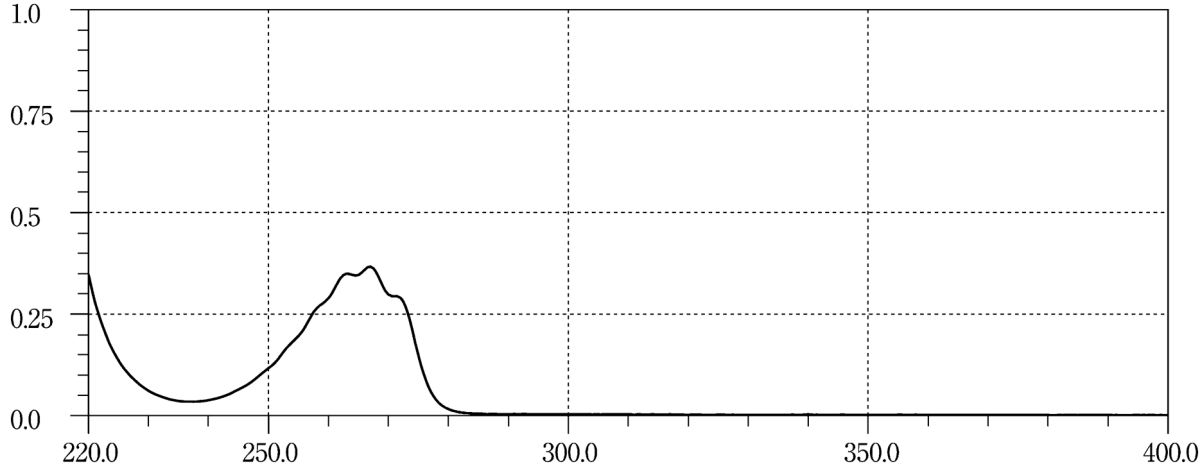
Irinotecan Hydrochloride Hydrate



Lanoconazole



Sitagliptin Phosphate Hydrate



General Information

GENERAL INFORMATION

G1 Physics and Chemistry

Add the following:

Control of Elemental Impurities in Drug Products

1. Introduction

Elemental impurities in drug products may arise from several sources; they may be residues intentionally added such as catalysts in the synthetic process of drug substances, drug substances being components of the drug product, impurities from natural products contained in additives, etc., and contaminants from manufacturing equipment and container/closure systems. The amounts of these impurities in drug products should be controlled within acceptable limits, except when they are stipulated in monographs.

The permitted daily exposures (PDEs) of elemental impurities are established to protect the health of all patients based on the evaluation of the toxic data of elemental impurities, and more strict limits are not needed if elemental impurities in drug products do not exceed the PDEs. In some cases, lower level of elemental impurities may be warranted when it is known that elemental impurities have been shown to have an impact on the quality attributes of the drug product (e.g., element catalyzed degradation of drug substances).

Elemental impurities in drug products are assessed and controlled based on a risk management approach.

2. Scope

The acceptable limit of elemental impurities apply to drug products, and also apply to drug products containing purified proteins and polypeptides (including proteins and polypeptides produced from genetic recombinant or non-recombinant origins), their derivatives, and drug products which they are components (e.g., conjugates) are within the scope of this guideline, as are drug products containing synthetic polypeptides, polynucleotides, and oligosaccharides.

It does not apply to crude drugs, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellar blood components, blood derivatives including plasma and plasma preparations, dialysate solutions not intended for systematic circulation, and drug products based on genes (gene therapy), cells (cell therapy) and tissues (tissue engineering). Also, it does not apply to elements that are intentionally included in the drug product for therapeutic benefit.

3. The PDEs for Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration, and Element Classification

The PDEs of elemental impurities established for preparations for oral, parenteral and inhalation routes of administration are shown in Table 1. If the PDEs for the other administration route are necessary, generally consider the oral PDE as a starting point in the establishment, and assess if the elemental impurity is expected to have local effects when administered by the intended route of administration.

Parenteral drug products with maximum daily volumes up to 2 L may use the maximum daily volume to calculate permissible concentrations from PDEs. For products whose daily volumes or general clinical practice may exceed 2 L (e.g., saline, dextrose, total parenteral nutrition, solutions for irrigation), a 2-L volume is used to calculate permissible concentrations from PDEs.

As shown in Table 1, elemental impurities are divided into three classes based on their toxicity (PDE) and likelihood of occurrence in the drug product. The likelihood of occurrence is judged from several factors, such as probabil-

Table 1 PDEs for Elemental Impurities

Element	Class	Oral PDE (μg/day)	Parenteral PDE (μg/day)	Inhalation PDE (μg/day)
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
TI	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

ity of use in pharmaceutical processes, impurities in materials used in pharmaceutical processes, the observed natural abundance and environmental distribution of the element.
Class 1: The elements, As, Cd, Hg, and Pb, are classified as this category and are human toxicant elements. As these elements are limited in the manufacture of pharmaceuticals, they are rarely used. Their presence in drug products usually comes from used materials such as mined excipients. These four elements require evaluation during the risk assessment, across all sources and routes of administration having possibility of contamination. Testing should only be applied when the risk assessment identifies it necessary to ensure that the PDE will be met, however it is not necessary for all components to determine for Class 1 elemental impurities.
Class 2: Elemental impurities classified as Class 2 have lower toxicity than the elements in Class 1, and are route-dependent human toxicants. These elements are further divided in 2A and 2B based on their relative likelihood of occurrence in the drug products. The class 2A elements are Co, Ni and V, which are known to exist naturally. These elements have relatively high probability of occurrence in drug products, and thus require evaluation during the risk assessment, across all sources and routes of administration having possibility of contamination. Because the Class 2B elements have the low probability of their existence in natural, they may be excluded from the risk assessment unless they are intentionally added during the manufacture of drug substances, excipients or other components of the drug product. The elemental impurities in Class 2B include Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl.
Class 3: The elements in this class have relatively low toxicities by the oral route of administration, and their oral PDEs are more than 500 μg/day. For oral routes of administration, unless these elements are intentionally added, they do not need to be considered during the risk assessment. For parenteral and inhalation products, the potential for inclusion of these elemental impurities should be evaluated even in the case where they are not intentionally added, unless the route specific PDE is above 500 μg/day. The elements in this class include Ba, Cr, Cu, Li, Mo, Sb and Sn.

4. Risk Assessment and Control of Elemental Impurities

The technique of quality risk management should be considered in controls for elemental impurities in drug products, and the risk assessment should be based on scientific knowledge and principles. The risk assessment would be focused on assessing the levels of elemental impurities in a drug product in relation to the PDEs. Useful information for this risk assessment includes measured data of drug products and components, measured data and the risk assessment result supplied by drug substance and/or excipient manufacturers, and/or data available in published literature, but is not limited to them.

The risk assessment should be performed depending on the level of risk, and do not always require a formal risk management process. The use of informal risk management processes may also be considered acceptable.

4.1. General Principles

The risk assessment process consists of the following three steps.

1) Identify known and potential sources of elemental impurities that may find their way into the drug product.

2) Evaluate the presence of a particular elemental impurity in the drug product by determining the observed or predicted level of the impurity and comparing with the established PDE.

3) Summarize the risk assessment, and identify if controls built into the process are sufficient. Identify additional controls to be considered to limit elemental impurities in the drug product.

In many cases, the steps are considered simultaneously. The risk assessment may be iterated to develop a final approach to ensure the elemental impurities do not exceed the PDE certainly.

4.2. Source of Elemental Impurities

In considering the production of a drug product, there are broad categories of potential sources of elemental impurities.

- Residual impurities resulting from elements intentionally added (e.g., metal catalysts) in the formation of the drug substance, excipients or other components. The risk assessment of the drug substance should be studied about the potential for inclusion of elemental impurities in the drug product.
- Elemental impurities that are not intentionally added and are potentially present in the drug substance, water or excipients used in the preparation of the drug product.
- Elemental impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment.
- Elemental impurities that have the potential to be leached into the drug substance and drug product from container closure systems.

During the risk assessment, the potential contributions from each of these sources should be considered to determine the overall contribution of elemental impurities to the drug product.

4.3. Identification of Potential Elemental Impurities

Potential elemental impurities derived from intentionally added catalysts and inorganic reagents: If any element is intentionally added, it should be considered in the risk assessment.

Potential elemental impurities that may be present in drug substances and excipients: While not intentionally added, some elemental impurities may be present in some drug substances and excipients. The possibility for inclusion of these elements in the drug product should be reflected in the risk assessment.

Potential elemental impurities derived from manufacturing equipment: The contribution of elemental impurities from this source may be limited and the subset of elemental impurities that should be considered in the risk assessment will depend on the manufacturing equipment used in the production of the drug product. The specific elemental

impurities of concern should be assessed based on the knowledge of the composition of the components of the manufacturing equipment that come in contact with components of the drug product. The risk assessment of this source of elemental impurities is one that can potentially be utilized for many drug products using similar process trains or processes.

In general, the processes used to prepare a given drug substance are considerably more aggressive than processes used in preparing the drug product when assessed relative to the potential to leach or remove elemental impurities from manufacturing equipment. Contributions of elemental impurities from drug product processing equipment would be expected to be lower than contributions observed for the drug substance. However, when this is not the case based on process knowledge or understanding, the potential for incorporation of elemental impurities from the drug product manufacturing equipment in the risk assessment (e.g., hot melt extrusion) should be considered.

Elemental impurities leached from container closure systems: The identification of potential elemental impurities that may be introduced from container closure systems should be based on a scientific understanding of likely interactions between a particular drug product type and its packaging. When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional risk assessment needs to be performed. It is recognized that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment. For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system during the shelf-life of the drug product. Studies to understand potential leachables from the container closure system (after washing, sterilization, irradiation, etc.) should be performed.

Factors that should be considered (for liquid and semi-solid dosage forms) are shown as follows, but are not limited.

- Hydrophilicity/hydrophobicity, Ionic content, pH, Temperature (cold chain vs room temperature and processing conditions), Contact surface area, Container/material composition, Terminal sterilization, Packaging process, Material sterilization, Duration of storage

Table 2 provides recommendations for inclusion of elemental impurities in the risk assessment. This can be applied to all sources of elemental impurities in the drug product.

4.4. Evaluation

As the potential elemental impurity identification process is concluded, there are following two possible outcomes.

1) The risk assessment process does not identify any potential elemental impurities.

2) The risk assessment process identifies one or more potential elemental impurities. For any elemental impurities identified in the process, the risk assessment should consider if there are multiple sources of the identified elemental impurity or impurities.

Table 2 Elements to be Considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	○	○	○	○
Pb	1	○	○	○	○
As	1	○	○	○	○
Hg	1	○	○	○	○
Co	2A	○	○	○	○
V	2A	○	○	○	○
Ni	2A	○	○	○	○
TI	2B	○	×	×	×
Au	2B	○	×	×	×
Pd	2B	○	×	×	×
Ir	2B	○	×	×	×
Os	2B	○	×	×	×
Rh	2B	○	×	×	×
Ru	2B	○	×	×	×
Se	2B	○	×	×	×
Ag	2B	○	×	×	×
Pt	2B	○	×	×	×
Li	3	○	×	○	○
Sb	3	○	×	○	○
Ba	3	○	×	×	○
Mo	3	○	×	×	○
Cu	3	○	×	○	○
Sn	3	○	×	×	○
Cr	3	○	×	×	○

○: necessary ×: unnecessary

During the risk assessment, a number of factors that can influence the level of the potential elemental impurity in the drug product should be considered.

4.5. Summary of Risk Assessment Process

The risk assessment is summarized by reviewing relevant product or component specific data combined with information and knowledge gained across products or processes to identify the significant probable elemental impurities that may be observed in the drug product.

The significance of the observed or predicted level of the elemental impurity should be considered in relation to the PDE of the elemental impurity. As a measure of the significance of the observed elemental impurity level, a control threshold is defined as a level that is 30% of the established PDE in the drug product. The control threshold may be used to determine if additional controls may be required.

If the total elemental impurity level from all sources in the drug product is expected to be consistently less than 30% of the PDE, then additional controls are not required, provided adequate controls on elemental impurities are demonstrated by the appropriate assessment of the data.

If the risk assessment fails to demonstrate that an elemental impurity level is consistently less than the control threshold, controls should be established to ensure that the

elemental impurity level does not exceed the PDE in the drug product.

The variability of the level of an elemental impurity should be factored into the application of the control threshold to drug products. Sources of variability may include the following.

- Variability of the analytical method
- Variability of the elemental impurity level in the specific sources
- Variability of the elemental impurity level in the drug product

For some components that have inherent variability (e.g., mined excipients), additional data may be needed to apply the control threshold.

5. Converting between PDEs and Concentration Limits

The PDEs reported in μg per day (μg/day) give the maximum permitted quantity of each element that may be contained in the maximum daily dose of a drug product. Because the PDE reflects total exposure from the drug product, it is useful to convert the PDE into concentrations as a tool in evaluating elemental impurities in drug products or their components. Any of the following options may be selectable as long as the resulting permitted concentrations assure that the drug product does not exceed the PDEs. In the choice of a specific option the daily dose of the drug product needs to be determined or assumed.

Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily doses of not more than 10 g: This option is not intended to imply that all elements are present at the same concentration, but rather provides a simplified approach to the calculations. The option assumes the daily dose of the drug product is 10 g or less, and that elemental impurities identified in the risk assessment (the target elements) are present in all components of the drug product. Using Equation (1) below and a daily dose of 10 g of drug product, this option calculates a common permissible target elemental concentration for each component in the drug product.

$$\text{Concentration } (\mu g/g) = \frac{PDE(\mu g/\text{day})}{\text{daily dose of drug product (g/day)}} \quad (1)$$

This approach, for each target element, allows determination of a fixed common maximum concentration in μg per g in each component. The permitted concentrations are provided in Table 3.

If all the components in a drug product do not exceed the Option 1 permitted concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product. If the permitted concentrations in Table 3 are not applied, Options 2a, 2b, or 3 should be followed.

Option 2a: Common permitted concentration limits of elements across drug product components for a drug product with a specified daily dose: This option is similar to Option 1, except that the drug daily dose is not assumed to be 10 g. The common permitted concentration of each element is determined using Equation (1) and the actual maximum daily dose. This approach, for each target element, allows determination of a fixed common maximum concentration in μg per g in each component based on the actual daily dose provided. If all components in a drug product do not exceed the Option 2a permitted concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product.

Option 2b: Permitted concentration limits of elements in individual components of a drug product with a specified daily dose: Permitted concentrations based on the distribution of elements in the components (e.g., higher concentrations in components with the presence of an element in question) may be set. For each element identified as potentially present in the components of the drug product, the maximum expected mass of the elemental impurity in the final drug product can be calculated by multiplying the mass of each component material times the permitted concentration pre-established in each material and summing over all components in the drug product, as described in Equation (2). The total mass of the elemental impurity in the drug product should comply with the PDEs unless justified according to other relevant sections of this general information. If the risk assessment has determined that a specific element is not a potential impurity in a specific component,

Table 3 Permitted Concentrations of Elemental Impurities for Option 1

Element	Class	Oral Concentration (μg/g)	Parenteral Concentration (μg/g)	Inhalation Concentration (μg/g)
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
TI	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

there is no need to establish a quantitative result for that element in that component. This approach allows that the maximum permitted concentration of an element in certain components of the drug product may be higher than the Option 1 or Option 2a limit, but this should then be compensated by lower allowable concentrations in the other components of the drug product. Equation (2) may be used to demonstrate that component-specific limits for each element in each component of a drug product assure that the PDE will be met.

$$PDE\ (\mu g/day) \geqq \sum_{k=1}^{N} C_k \cdot M_k \qquad (2)$$

k = an index for each of N components in the drug product

C_k = permitted concentration of the elemental impurity in component k ($\mu g/g$)

M_k = mass of component k in the maximum daily dose of the drug product (g)

Option 3: Finished Product Analysis: The concentration of each element may be measured in the final drug product. Equation (1) may be used with the maximum total daily dose of the drug product to calculate a maximum permitted concentration of the elemental impurity.

6. Speciation and Other Considerations

Speciation is defined as the distribution of elements among chemical species based on the difference of molecular structure including ionic element, molecules, or complexes, reflecting isotopic composition, electronic or oxidation state. When the toxicities of different species of the same element are known to be different, the PDE has been established using the toxicity information on the species expected to be in the drug product.

When elemental impurity measurements are used in the risk assessment, total elemental impurity levels in drug products may be used to assess compliance with the PDEs. The identification of speciation is not particularly expected, however such information could be used to justify lower or higher levels when the identified species is more or less toxic, respectively, than the species used for the calculation of the PDEs.

When total elemental impurity levels in components are used in the risk assessment, providing information on release of an elemental impurity from the component in which it is found is not expected. However, such information could be used to justify levels higher than those based on the total elemental impurity content of the drug product.

7. Analytical Procedures

The determination of elemental impurities should be conducted using appropriate procedures suitable for their intended purposes. Unless otherwise justified, the test should be specific for each elemental impurity identified for control during the risk assessment. Elemental Impurities-Procedures <*2.66*> or suitable alternative procedures for determining levels of elemental impurities should be used.

8. Lifecycle Management

If changes to the drug product or components have the potential to change the elemental impurity content of the drug product, the risk assessment, including established controls for elemental impurities, should be re-evaluated. Such changes could include changes in synthetic routes, excipient suppliers, raw materials, processes, equipment, container closure systems or facilities.

G3 Biotechnological/Biological Products

Add the following:

Host Cell Protein Assay

Host cell protein (HCP) is a general term for proteins derived from host cells used for the production of pharmaceutical products. This general information describes HCP assays for therapeutic proteins produced by recombinant DNA technology (recombinant therapeutic proteins).

Residual HCP in recombinant therapeutic proteins has potential to elicit immune responses against itself and may also act as adjuvants to induce anti-drug antibodies. Therefore, in order to ensure the efficacy and safety of recombinant therapeutic proteins, it is necessary to establish a purification process to reduce HCP to a level that does not affect safety. In addition, residual levels of HCP must be appropriately controlled by verifying that in-process tests can consistently eliminate HCP or by establishing purity testing of drug substance.

1. Selection of Test Methods for HCP assay

HCP assay is usually performed with a sandwich immunoassay using antibodies against HCP (anti-HCP antibodies) and detection systems including enzyme-linked immunosorbent assay (ELISA), electrochemiluminescent immunoassay (ECLIA), and time-resolved fluorescent immunoassay (TRFIA). This general information addresses the sandwich immunoassay, but does not discourage other assays.

Residual HCP from the manufacturing process of recombinant therapeutic proteins consists a large number of proteins and may have profiles that vary from one host cell to another or depending on manufacturing conditions. Based on differences in its intended use or differences in the concept of preparation of anti-HCP antibodies used for testing, HCP assay is classified into generic assay, product-specific assay, and platform assay. Generic assay is intended for wide use in pharmaceutical products manufactured using similar host cells (e.g., CHO-K1 or CHO-DG44 cells derived from CHO [Chinese hamster ovary] cells) and is a test method established using anti-HCP antibodies that are prepared with proteins from all conponents of the host cells (cell lysate or culture supernatant) as immunogens. Commercially available reagents or kits for an HCP assay com-

monly referred to as generic assay and need to be validated before use. Product-specific assay is intended to control HCP in a specific product and developed in consideration of characteristics of the manufacturing process of the product. Platform assay is developed for the application to recombinant therapeutic proteins (e.g., monoclonal antibodies with adequate experience) produced by a manufacturing platform.

Generic assay is intended to comprehensively obtain antibodies against a wide range of HCP by using proteins from all conponents of the host cells as antigens. However, it should be noted that it is difficult to obtain antibodies against all HCPs because of differences in proportions or immunogenicity of individual proteins used as antigens and that residual HCP from actual manufacturing processes may be inadequately covered because of potential different profiles of residual HCP from different manufacturing processes. In contrast, product-specific assay is expected to prepare anti-HCP antibodies that can detect residual HCP from actual manufacturing processes compared with generic assay because it uses potentially residual HCP as antigens. However, it should be noted that profiles of residual HCP may vary with modifications to manufacturing processes. Platform assay has both aspects, namely, the assay has an advantage of being able to be applied to various products prepared by a manufacturing platform; however, the assay may involve issues as generic or product-specific assay, depending on the method of preparation of antigens used for preparing anti-HCP antibodies.

In some products, it is possible that specific HCPs binding to desired products are present or that HCPs markedly increase in production amount with expression of desired products. If the residue of these HCPs is found, the need to establish other test methods for the HCPs is considered.

In light of these characteristics of the test methods for HCP assays and in consideration of properties of host cells, characteristics of manufacturing processes, knowledge about immunogenicity of HCPs, stages of development of products, etc., an appropriate test method is selected.

2. Preparation and Characterization of Reagents

2.1. HCP Antigens/HCP Reference Materials

For antigens to produce antibodies that specifically detect HCPs in products, it is necessary to prepare HCP not containing desired products. Usually, null cells are used for preparation of HCP antigen while keeping in mind that HCP appropriate to the purpose of the HCP assay are comprehensively contained. In addition, HCP are used not only as antigens but also as reference materials for HCP assay and may also be used as ligands for purification of anti-HCP antibodies by affinity chromatography.

2.1.1. Preparation of HCP Antigens/HCP Reference Materials

The method of preparation of HCP antigens/HCP reference materials varies widely depending on the type of test methods. The method of preparation of HCP used as antigens for preparation of anti-HCP antibodies or as HCP reference materials in the test methods is shown below along with points to note.

HCP used for generic assays are prepared from culture supernatant or lysed or disrupted null cells using minimal procedures such as concentration and dialysis and keeping preservation of component proteins in mind. It should be noted that these HCPs show profiles that are different from those of residual HCP in products because of preparation under conditions different from culture processes at commercial scale.

HCP used for product-specific assays are prepared from null cells using manufacturing processes of products. Usually, the application of the purification process is minimized to obtain a wide range of HCP. However, if a suitable antibody to detect the HCP is not obtained, it may be necessary to prepare appropriate HCP antigens by exploring conditions of preparation of HCP or excluding specific HCP.

HCP used for the platform assays are prepared from null cells using a manufacturing platform that can be used in multiple products. Usually, as with the other test methods, the application of the purification process is minimized to obtain a wide range and an enough amount of HCP. In addition, a mixture of HCPs prepared under multiple conditions can be used to address differences in HCP spectra due to slight differences in manufacturing conditions.

The use of mock cells as null cells used for preparation of HCP for product-specific and platform assays has advantages such as the presence of proteins expressed as selection markers in antigens and ability to culture the cells under similar culture conditions in actual manufacturing processes. In contrast, it should be noted that even a same cell line does not show consistent properties (such as cell growth rate) among different clones and that differences such as the presence or absence of production of desired products may cause different profiles of HCP.

2.1.2. Characterization of HCP Antigens/HCP Reference Materials

Prepared HCPs are analyzed for the following items.

1) Protein Concentrations

Protein concentrations are determined by a suitable measurement method keeping in mind that host cell nucleic acids or culture medium components may be contained depending on the method of preparation of HCP. For information on detailed measurement methods and points to consider, ''Protein Assay'' in General Information would be helpful.

2) HCP Profiles

Usually, one-dimensional electrophoresis (SDS-PAGE) or two-dimensional electrophoresis is used to confirm that prepared HCP include HCP species that are considered to remain in manufacturing processes or drug substances. Identification of HCP species by mass spectrometry is also a helpful approach.

2.2. Anti-HCP Antibodies

2.2.1. Preparation of Anti-HCP Antibodies

Since HCPs represent a heterogeneous variety of different proteins, polyclonal antibodies are obtained as anti-HCP antibodies used for the assay to comprehensively detect HCPs. The rabbit, goat, and sheep are commonly used animal species for immunization. For immunization, it is

useful to enhance immune response with adjuvants. Due to different degrees of immunogenicity of individual proteins comprising HCPs, the timing of induction of antibodies or the amount of antibodies produced is not constant, regardless of the amount of proteins as antigens. In addition, inter-individual variability in animals used for immunization makes the profile of induced antibodies inconsistent. Several rounds of immunization are usually required and, after determining the reactivity of induced antibodies with HCPs by Western blotting using antisera in each period of immunization, whole serum is collected. Mixing of anti-HCP antibodies derived from multiple individuals is intended to obtain adequate amounts of antibodies and is also expected to contribute to the elimination of imbalance of HCP profiles.

Anti-HCP antibodies are purified from the obtained antiserum by Protein A or Protein G chromatography. In either case, aggregates may be formed from some antibodies due to use of acid conditions for antibody elution from the columns. It is useful to remove antibody aggregates by a suitable method because they may cause interference with measurement.

Anti-HCP antibodies can also be purified by affinity chromatography using HCP as ligands. This purification is expected to eliminate non-specific reactions because of concentration of antibodies specific to HCPs, however, it should be noted that anti-HCP antibodies may get less diverse due to less adsorption of low-affinity antibodies or less elution of very high-affinity antibodies.

2.2.2. Suitability of Anti-HCP Antibodies

Anti-HCP antibodies have to be able to comprehensively recognize HCPs with wide ranges of electric charges and molecular masses that potentially remain in manufacturing processes or drug substances. However, because differences in immunogenicity of each HCP species may make antibodies against some HCPs less likely to be induced, obtained anti-HCP antibodies have to be qualified, usually as measured by antigen coverage. A specific example of assessment methods is shown below. After separation of HCPs by two-dimensional electrophoresis, total protein on the gel is stained. After performing two-dimensional electrophoresis in the same manner, Western blotting using anti-HCP antibodies is performed. Spot patterns obtained from each staining are compared and the proportion of spots detected by Western blotting vs spots obtained in total protein staining is determined as antigen coverage.

2.3. Storage of Reagents

HCP reference materials and anti-HCP antibodies are stored with attention to stability. The stability of these reagents can be confirmed by continuously monitoring parameters of dose-response curves of reference materials.

3. Validation of HCP Assay

When a sandwich immunoassay is used for HCP assay, ''Validation of Analytical Procedures'' in General Information would be helpful for information on basic requirements for validation. However, unlike a conventional sandwich immunoassay to determine a single antigen, HCP assay is an approach to use antibodies prepared with a mixture of various HCP species as antigens to determine the HCP species simultaneously. Therefore, changes in concentrations as a function of dilution ratios of samples (dilution linearity) may not be observed in highly purified samples even within the quantitation limits in which linearity has been obtained for HCP reference materials. This phenomenon is likely attributed to insufficient amounts of antibodies to some HCPs that are found in increased proportions in samples for measurement due to the difference of removal rates of individual HCPs in the purification process and may lead to underestimation of HCP concentrations.

Therefore, HCP assay should be validated for accuracy, precision, specificity, standard curve, quantitative range, and dilution linearity.

(1) Accuracy and Precision

Accuracy and precision are expressed as coefficients of variation of recovery rates and quantitative values of HCP reference materials, respectively, by performing spike and recovery tests of HCP reference materials in purification process pools or drug substances to be measured.

(2) Specificity

Because HCP assay involves measurement of trace amounts of HCPs remaining in samples containing large quantities of desired products, it should be confirmed that there is no interference of desired substances or ingredients in sample solutions.

(3) Standard Curve and Quantitative Range

A standard curve is generated using serially diluted HCP reference materials, a regression expression is obtained, and validity is expressed in terms of determination coefficient, etc. Quantitative values of reference materials at each concentration level are determined from the regression expression and a range of concentrations with acceptable levels of accuracy and precision is defined as quantitative range with the lowest concentration within the range being defined as the minimum limit of quantitation.

(4) Dilution Linearity

Purification process pools or drug substances to be measured are examined for the range of dilution ratios of samples in which quantitative values of samples diluted within the quantitative range of a standard curve are linear.

4. Establishment of HCP Assay

HCP assay is used for confirmation of the status of removal of HCP in manufacturing processes or as a purity test of drug substances. For information on basic concepts of procedures or data analysis in HCP assay, ''Enzyme-linked Immunosorbent Assay'' in General Information would be helpful.

Results from HCP assay are usually presented as contents in desired products. Contents of HCP per total protein or desired products can be determined by separately determining concentrations of the proteins in samples. For example, when total protein concentration is 2 mg/mL and an HCP concentration is 20 ng/mL, the content of HCP should be indicated as 10 ng/mg.

5. Others

5.1. Considerations for Modifications to Manufacturing Processes

Since any modifications made to manufacturing processes for recombinant therapeutic proteins may affect profiles of residual HCP, it is necessary to confirm that appropriate measurement of HCP is performed after modifications to manufacturing processes. If HCP profiles are altered and it is considered inappropriate to apply a test method for HCP assay before modifications to manufacturing processes, a test method for HCP assay has to be established again. Changes in HCP profiles can be assessed by an analytical procedure such as two-dimensional electrophoresis or mass spectrometry.

5.2. Considerations for Modifications to Reagents for Tests

It is desirable to secure sufficient quantities of HCP antigens/HCP reference materials and anti-HCP antibodies, all important reagents, whenever possible, in consideration of the life cycle of products. When HCP antigens/HCP reference materials or anti-HCP antibodies are newly prepared, it should be confirmed that their characteristics are comparable before and after renewal by analytical procedures such as two-dimensional electrophoresis, Western blotting, and mass spectrometry. In addition, test methods should be validated again for necessary items and newly prepared reagents should be used after confirming their consistency with the reagents and test methods before renewal.

When generic assay is employed, qualified commercially available kits can also be used. However, availability of information on lot renewal of reagents, etc. is necessary to ensure consistency and quality of tests using commercially available kits, and therefore characterization of important reagents and method validation should be performed as needed.

6. Terms

Mock cell: A cell line established from the host cell line by transferring expression vectors that do not contain genes encoding desired products.

Null cell: A host cell that does not express desired products. It includes parent cells or mock cells.

Antigen coverage: The rate of detection of proteins comprising HCPs by anti-HCP antibodies. For example, an antigen coverage can be calculated from the number of spots obtained in total protein staining and the number of spots obtained in Western blotting using anti-HCP antibodies after separation of HCPs by two-dimensional electrophoresis.

Total Protein Assay

Delete the description of harmonization in the beginning and symbols (◆ ◆).

G4 Microorganisms

Delete the following items:

Media Fill Test (Process Simulation)

Microbiological Environmental Monitoring Methods of Processing Areas for Sterile Pharmaceutical Products

Parametric Release of Terminally Sterilized Pharmaceutical Products

G5 Crude Drugs

Purity Tests on Crude Drugs using Genetic Information

Change the following as follows:

The first step in the quality assurance of natural products is the use of raw materials from the right part of the right origin. Therefore, it is clearly stated in Article 4 of the General Rules For Crude Drugs that the source of a crude drug is an approval or rejection criterion. There are various methods for differentiating the sources of crude drugs, such as morphological methods, organoleptic tests, and chemical methods, and appropriate methods for each are described in the individual monographs. Morphological methods, organoleptic tests, and chemical methods are discrimination methods for species that are based on the phenotypic characteristics of the crude drugs. On the other hand, together with recent progress in molecular biology techniques and the accumulation of genetic information on plants, differentiating methods of crude drugs based on genotypes is being established. Unlike morphological and other methods that are based on phenotypic characteristics, the genotypic methods are not affected by environmental factors. Also, the methods have several advantages, such as specialized expertise and skill for classification are not needed, and objective results are easily obtained.

The evolution of living organisms is accomplished by genetic mutation, and differences among the nucleotide sequences of genes of closely related species reflect the strain relationships between the species. Based on this theory, methods that classify species phylogenetically using the nucleotide sequence of rDNA that codes for ribosomal RNA (rRNA) on the nuclear genome have recently been adopted for the classification of microorganisms. In the same way, the sequence of this rDNA is also most often

used in the classification of higher plants based on the genotype. In particular, it is very easy to classify closely related species using the internal transcribed spacer (ITS) region of the rDNA, since nucleotide substitution is more often undertaken by comparison with the coded gene region. Furthermore, since the genes on the nuclear genome originate from the parents' genomes, there is an advantage that interspecies hybrids can be detected. Higher plants also have mitochondrial genes and chloroplastic genes. Although the genes on these genomes are also often used for classification, interspecies hybrids cannot be confirmed because the genes are normally uniparental inheritance.

The three methods presented here are, 1) the purity test of Atractylodes Rhizome for Atractylodes Lancea Rhizome, 2) the purity test of Saposhnikovia Root and Rhizome for *Peucedanum ledebourielloides*, which are developed based on the difference of the gene sequence of the ITS region of rDNA recently reported[1-4], and the inter-laboratory validation study have been completed.

The plant sources for Atractylodes Lancea Rhizome stipulated in the individual monographs are *Atractylodes lancea* De Candolle and *A. chinensis* Koidzumi (*Compositae*), while those for Atractylodes Rhizome are *A. japonica* Koidzumi ex Kitamura and *A. macrocephala* Koidzumi (*Compositae*). The approval or rejection of the both sources is, in principle, determined by the description of the crude drug, including microscopy, together with thin-layer chromatography in identification tests. In the above scientific paper, it was shown that these 4 plant species can be clearly classified by comparing the nucleotide sequences of the ITS region mentioned above, and that the species can be easily classified without performing sequence analysis by performing PCR using a species-specific primer pair or by using a restriction enzyme which recognizes species-specific sequence.

Likewise, the plant source of Saposhnikovia Root and Rhizome is stipulated as *Saposhnikovia divaricata* Schischkin (*Umbelliferae*), and the approval or rejection of the source is determined by the description of the crude drug and thin-layer chromatography in identification tests. According to the report[4], crude drugs treated as Saposhnikovia Root and Rhizome in Shaanxi and Shanxi Provinces are frequently derived from *Peucedanum ledebourielloides*, and it was shown that the differentiation of the both is possible by using the nucleotide sequence in the ITS region of the rDNA.

In purity tests on crude drugs using genetic information, the simplicity of the test is given maximum consideration. We established methods that observe PCR amplification bands using species-specific primer pair (Mutant Allele Specific Amplification: Method 1) and methods that observe DNA fragments produced by restriction enzyme treatment of the PCR products, which are prepared using a primer pair common to each plant source (PCR—Restriction Fragment Length Polymorphism: Method 2), without nucleotide sequence analyses. In these methods based on PCR, an extremely small amount of template DNA is amplified to billions to hundreds of billions times. Therefore, when using them as identification tests for powdered crude drugs, the target DNA fragment can be observed even if the vast majority of the crude drug for analysis is not appropriate plant species and there is only a minute amount of powder from a crude drug derived from a suitable plant. Consequently, in identification tests, either a cut or a whole crude drug must be used, as long as one is careful to avoid contamination by powder originating from other crude drugs. On the other hand, when used as a purity test, the form of the crude drug is irrelevant as long as the gene amplification is performed properly and the target gene is not polymorphic, so if DNA fragments of an inappropriate plant to be examined are confirmed in the purity test, regardless of the form of the crude drug, it becomes clear there is contamination by an inappropriate crude drug to be examined.

The methods shown here are general information and at the present stage results obtained using the methods do not affect the approval or rejection of the crude drug in each monograph. Furthermore, by performing the sequence analysis outlined in the previous paper for a crude drug sample derived from a single individual, it goes without saying that more accurate decision concerning the source species can be made.

1. DNA Amplification Equipment

DNA amplification equipment is used to amplify the DNA which is extracted from a crude drug and then purified. Since there are slight differences in the methods of temperature control, and so on depending on the equipment used, there may be differences in the intensity, etc. of the PCR amplification bands even if PCR is carried out under the stipulated conditions. Therefore, when judging results based solely on the presence or absence of PCR amplification bands as in Methods 1, the use of equipment described in the JAS analytical test handbook: genetically modified food quality, labeling analysis manual for individual products[5] is recommended. When other equipment is used, confirm that only proper amplification bands are obtained by performing PCR using DNA obtained from samples confirmed beforehand to be the source species. If proper amplification bands are not obtained, the PCR temperature conditions should be slightly adjusted. This equipment can be used for the restriction enzyme treatment in Method 2.

2. General precautions

Crude drugs are different from fresh plants in that they are dried products and a certain amount of time has passed since they were harvested. Therefore, in many cases the DNA has undergone fragmentation. Furthermore, various substances that can block or interfere with the PCR reaction may be present in the plant. For these reasons, the extraction and purification of template DNA is the process that should receive the greatest amount of attention. In the case of Atractylodes crude drugs, the periderm should be removed using a clean scalpel or other clean instrument before pulverizing the sample because very often there are inhibitory substances present in the periderm.

The PCR used for this test is the technique that amplify the target DNA more than hundreds of millions times, and

a trace of contamination leads an incorrect result. Therefore, careful attention is required to prevent contamination. For treatment to prevent contamination, refer to the prevention of contamination section[6] in the above manual.

3. Purity test of Atractylodes Rhizome for Atractylodes Lancea Rhizome

3.1. Method 1 (Mutant Allele Specific Amplification Method)

Generally, this method is referred to as Mutant Allele Specific Amplification (MASA) or Amplification Refractory Mutation System (ARMS), and it provides nucleotide sequence information of sample-derived template DNA, based upon the presence or absence of DNA amplification in PCR using a species specific primer pair.

3.1.1. Procedure

The following is an example procedure.

3.1.1.1. Preparation of template DNA

There are various methods with which to extract and purify DNA from the samples. It is recommended that commercially available DNA extraction kits be used when considering their advantages of not using any noxious reagents and not requiring any complicated purification procedures. In this case, attention should be paid to the final amount (concentration) of DNA obtained, and the initial amount of initial sample and the volume of liquid to elute the DNA need to be controlled. When extraction and purification are performed using silica gel membrane type kits stipulated in notifications[7] related to inspection methods of the foods produced by recombinant DNA techniques, it is appropriate to use 200 mg of sample, 1 mL of AP1 buffer solution, 2 μL of RNase A, and 325 μL of AP2 buffer solution. Also, the most important things are that the supernatant loaded on the first column is clear and that there is no need to load 1 mL unreasonably. Furthermore, 50 μL is an appropriate volume used in the final elution of the DNA, and normally the initial eluate is used as the DNA sample stock solution.

3.1.1.2. Confirmation of purity of DNA in DNA sample stock solution and assay of DNA

The purity of the DNA in the stock solution can be confirmed by the $OD_{260\,nm}/OD_{280\,nm}$ ratio using a spectrophotometer. A ratio of 1.5 indicates that the DNA has been adequately purified. The amount of DNA is calculated using 1 $OD_{260\,nm}$ = 50 μg/mL. The measurement mentioned above is performed using appropriately diluted DNA sample stock solution. Based on the results obtained, dilute with water to the concentration needed for the subsequent PCR reactions, dispense the solution into micro tubes as the sample DNA solution, and if necessary store frozen at not over −20°C. The dispensed DNA sample is used immediately after thawing and any remaining solution should be discarded and not refrozen. If the concentration of the DNA sample stock solution does not reach the concentration stipulated in PCR, it is used as a DNA sample solution.

3.1.1.3. PCR

When a commercially available PCR enzyme mentioned in the above notification[8] is used, it is appropriate that 25 μL of reaction mixture consisting of 2.5 μL of the PCR buffer solution containing magnesium, dNTP (0.2 mmol/L), 5′ and 3′primer (0.4 μmol/L), Taq DNA polymerase (1.25 units), and 5 μL of 10 ng/μL sample DNA solution (50 ng of DNA) is prepared on ice. Among them, the PCR buffer solution and dNTP are provided as adjuncts to the enzyme. When conducting purity tests on Atractylodes Lancea Rhizome in Atractylodes Rhizome, the primer sets used are C and D (C is positive with *A. lancea*, D is positive with *A. chinensis*) as described in the paper[1] mentioned above, however, when primer sets A and B are used, it is possible to confirm the source species of each of the respective specimens. In order to confirm that the DNA has been extracted correctly, the reaction solution containing the positive control primer pair (Pf and Pr) as shown below should be prepared. In addition, the negative control solutions which are not containing DNA sample or either of the primer pair should be prepared and simultaneously conduct PCR.

Pf: 5′-CAT TGT CGA AGC CTG CAC AGC A-3′
Pr: 5′-CGA TGC GTG AGC CGA GAT ATC C-3′

The PCR reaction is performed under the following conditions: starting the reaction at 95°C for 10 minutes, 30 cycles of 0.5 minutes at 95°C and 0.75 minutes at 68°C (69°C only when using the primer set C), terminate reaction at 72°C for 7 minutes, and store at 4°C. The resulting reaction mixture is used for the following process as PCR amplification reaction solution.

3.1.1.4. Agarose gel electrophoresis and detection of PCR products

After completion of the PCR reaction, mix 5 μL of the PCR amplification reaction solution with an appropriate volume of gel loading buffer solution, add the mixture to the wells of 2 w/v% agarose gel, and then perform electrophoresis using 1-fold TAE buffer solution (refer to General Information, Rapid Identification of Microorganisms Based on Molecular Biological Method). Carry out the electrophoresis together with an appropriate DNA molecular marker. Electrophoresis is terminated when the bromophenol blue dye in the gel loading buffer has advanced to a point corresponding to 1/2 to 2/3 the length of the gel.

Stain the gel after electrophoresis when not using gel stained in advance with ethidium bromide. Place the gel that has undergone electrophoresis and staining in a gel image analyzer, irradiate with ultraviolet light (312 nm), and detect its electrophoresis pattern. Compare this to the DNA molecular marker and determine the absence or presence of the target amplification band.

3.1.2. Judgment

Confirm at first that a 305 bp band is found with the reaction solution to which the positive control primer pair has been added, and confirm there are no bands in a solution with no primer sets and a solution with no sample DNA solution. Next, if a 226 bp band is confirmed when the primer set C is added or if a 200 bp band is confirmed when the primer set D is added, the sample is judged to be Atractylodes Lancea Rhizome (in the case of cut crude drug, contamination of Atractylodes Lancea Rhizome is observed)

and it is rejected. The sample is judged not to be Atractylodes Lancea Rhizome (in the case of cut crude drug, there is no contamination of Atractylodes Lancea Rhizome) and the purity test is acceptable if a 305 bp band is confirmed with the positive control primer pair, bands are not observed in reaction solution without primer and reaction solution without DNA sample solution, and a 226 bp band is not observed with the primer set C and a 200 bp band is not observed with the primer set D. If a band is not observed with the positive control primer pair, it is to be concluded that the DNA extraction failed and the procedure should be started over again from the DNA extraction step. If bands are confirmed in reaction solutions without primer sets or without DNA sample solution, it should be assumed that there was an error in the PCR procedure and therefore the procedure should be repeated again from the step 3.1.1.3. PCR.

3.2. Method 2 (PCR—Restriction Fragment Length Polymorphism)

Generally, this method is referred to as PCR—Restriction Fragment Length Polymorphism (RFLP), and it provides nucleotide sequence information of sample-derived template DNA, based upon the DNA fragment pattern produced by restriction enzyme treatment of the PCR products, which are amplified by using a primer pair common to the DNA sequence of the objective plant.

The test is performed with 25 samples randomly taken from a lot, and each sample is designated with a number from 1 to 25. Differentiation of the sources is performed by individual PCR—RFLP measurement of the samples, and decision of the acceptability of the purity is dependent on how many nonconforming samples are present in the first 20 samples, taken in numerical order, for which judgment is possible as described below.

3.2.1. Procedure

The following is an example procedure.

3.2.1.1. Preparation of template DNA

There are various methods with which to extract and purify DNA from the samples. It is recommended that commercially available DNA extraction kits be used, when considering their advantages of not using noxious reagents and not requiring complicated purification procedures. Recently, PCR reagents that inhibit the effect of PCR enzymeinhibiting substances present in samples have become commercially available, and by using these reagents, it is possible to prepare the template DNA from the sample simply by incubating the sample with the DNA extraction reagent. Here, a recommended DNA preparing procedure using such PCR reagents is described for the convenience of experimenters.

Cut 20 mg of the sample into small pieces with a clean knife, add 400 μL of the DNA extraction reagent, and incubate at 55°C overnight (16 – 18 hours). Then heat at 95°C for 5 minutes to inactivate the enzyme in the reagent. Centrifuge to precipitate the sample, and use 50 μL of the supernatant liquid as the template DNA solution. The DNA solution prepared in this method can not be used for concentration measurement based on $OD_{260\,nm}$, because it contains many foreign substances affecting $OD_{260\,nm}$ value from the sample.

The composition of the DNA extraction reagent is as follows:

2-Amino-2-hydroxymethyl-1,3-propanediol-hydrochloric acid (pH 8.0)	20 mmol/L
Ethylenediamine tetraacetate	5 mmol/L
Sodium chloride	400 mmol/L
Sodium dodecyl sulfate	0.3%
Proteinase K	200 μg/mL

3.2.1.2. PCR

In the method using the PCR enzyme and PCR reagent as described[3)], the reaction mixture is prepared on an ice bath in a total volume of 20 μL of a solution containing 10.0 μL of 2-fold concentrated PCR reagent, 5′- and 3′-primers (0.5 μmol/L), Taq DNA polymerase (0.5 units) and 0.5 μL of template DNA solution.

The PCR reaction is performed under the following conditions: 95°C for 10 minutes, 40 cycles of 95°C for 0.5 minute, 65°C for 0.25 minute, and 72°C for 0.25 minute and 72°C for 7 minutes. Store the solution at 4°C, and use this solution as the PCR amplified solution. A negative control (containing water instead of the template DNA solution) must be included in the procedure.

The sequence of each primer is as follows:

5′-primer: 5′-GGC ACA ACA CGT GCC AAG GAA AA-3′

3′-primer: 5′-CGA TGC GTG AGC CGA GAT ATC C-3′

3.2.1.3. Restriction enzyme treatment

The treatment is performed on individual reaction solutions using two enzymes, *Fau* I and *Msp* I. In the case of *Fau* I, to an appropriate amount of the reaction solution, composed of a reaction buffer containing 1.0 unit of enzyme, add 3.0 μL of PCR products while cooling in an ice bath to make 15.0 μL. In the case of *Msp* I, to an appropriate amount of the reaction solution, composed of a reaction buffer containing 20.0 units of enzyme, add 3.0 μL of PCR products while cooling in an ice bath to make 15.0 μL. Incubate these solutions at the temperature recommended by the manufacturer for 2 hours, and then inactivate the enzyme by heating at 72°C for 10 minutes. The negative control of the PCR reaction is also treated in the same manner.

3.2.1.4. Agarose gel electrophoresis and detection of DNA fragments

After the restriction enzyme treatment, mix the total amount of the reaction solution and an appropriate amount of the gel loading buffer solution, place it in a 4 w/v% agarose gel well, and carry out electrophoresis with 1-fold concentrated TAE buffer solution (see ''Rapid Identification of Microorganisms Based on Molecular Biological Methods'' under General Information). Carry out the electrophoresis together with appropriate DNA molecular marker. Stop the electrophoresis when the bromophenol blue included in the loading buffer solution has moved about 2 cm from the well. The 4 w/v% agarose gel is sticky, difficult

to prepare and hard to handle, so that it is better to use a commercially available precast gel.

After the electrophoresis, stain the gel, if it is not already stained, with ethidium bromide, and observe the gel on an illuminating device under ultraviolet light (312 nm) to confirm the electrophoretic pattern.

3.2.2. Judgment

3.2.2.1. Judgment of each sample

Confirm that no band is obtained with the negative control of the PCR, other than the primer dimer (about 40 bp) band. A sample treated with *Fau* I, showing bands of about 80 bp and 60 bp, or that treated with *Msp* I, showing bands of about 90 bp and 50 bp, is judged as Atractylodes Lancea Rhizome. A sample not showing any band other than a band at about 140 bp and the primer dimer band is judged as Atractylodes Rhizome. If a sample does not show any band other than the primer dimer band, it is considered that PCR products were not obtained, and judgment is impossible for the sample.

3.2.2.2. Judgment of the purity

Judgment of the purity is based on the result of the judgment of each sample. If there is no sample that is judged as Atractylodes Lancea Rhizome among 20 samples taken in order of the numbering, excluding any sample for which judgment is impossible, the lot is acceptable for purity. When there is one sample that is judged as Atractylodes Lancea Rhizome among the 20 samples, perform the same test with 25 newly taken samples from the lot, and if there is no sample that is judged as Atractylodes Lancea Rhizome, the lot is acceptable for purity. When there is a sample that is judged as Atractylodes Lancea Rhizome in the second test, or there is more than one sample that is judged as Atractylodes Lancea Rhizome in the first test, the lot is not acceptable for purity.

4. Purity test of Saposhnikovia Root and Rhizome for *Peucedanum ledebourielloides*

4.1. Method 1

Similarly as 3.1., this method provides nucleotide sequence information of sample-derived template DNA, based upon the presence or absence of DNA amplification band in PCR using a species specific primer pair.

4.1.1. Procedure

The following is an example procedure.

4.1.1.1. Preparation of template DNA

For Atractylodes crude drugs, a preparation procedure using a silica gel membrane type kit is adopted, however for the test of Saposhnikovia Root and Rhizome, and *Peucedanum ledebourielloides*, the simple preparation procedure shown below is adopted for the convenience of experimenters, because it was confirmed that the PCR product is stably obtained in using a DNA sample solution prepared by the simple preparation procedure shown in 3.2.1.1. as a template.

Cut 10 mg of the sample into small pieces with a clean knife, add 400 μL of the DNA extraction reagent, and incubate at 55°C overnight (16 – 18 hours). Then heat at 95°C for 5 minutes to inactivate the enzyme in the reagent. Centrifuge to precipitate the sample, and use 50 μL of the supernatant liquid as the template DNA solution. The DNA solution prepared in this method can not be used for concentration measurement based on OD_{260nm}, because it contains many foreign substances affecting OD_{260nm} value from the sample.

The composition of the DNA extraction reagent is as follows:

2-Amino-2-hydroxymethyl-1,3-propanediol-hydrochloric acid (pH 8.0)	20 mmol/L
Ethylenediamine tetraacetate	5 mmol/L
Sodium chloride	400 mmol/L
Sodium dodecyl sulfate	0.3%
Proteinase K	200 μg/mL

4.1.1.2. PCR

In the method using the PCR enzyme and PCR reagent as described[3], the reaction mixture is prepared on an ice bath in a total volume of 20 μL of a solution containing 10.0 μL of 2-fold concentrated PCR reagent, 5′- and 3′-primers (0.5 μmol/L), Taq DNA polymerase (0.5 units) and 0.5 μL of template DNA solution.

When the purity test of Saposhnikovia Root and Rhizome for *Peucedanum ledebourielloides* is performed, the reaction solution containing the positive control primer pair as shown below should be prepared besides the reaction solution containing a species specific primer pair in order to confirm that the DNA has been extracted correctly. In addition, the negative control solutions which are not containing DNA sample should be prepared and simultaneously conduct PCR.

The PCR reaction is performed under the following conditions: 95°C for 10 minutes, 45 cycles of 95°C for 0.5 minute, 62°C for 0.5 minute, and 72°C for 0.75 minute and 72°C for 7 minutes. Store the solution at 4°C, and use this solution as the PCR amplified solution. The sequence of each primer is as follows. The positive control 3′-primer for PCR and the species specific 3′-primer for PCR have the same sequence.

5′-primer for positive control PCR: 5′-GCG TGG GTG TCA CGC ATC G-3′

3′-primer for positive control PCR: 5′-GTA GTC CCG CCT GAC CTG-3′

5′-primer for species specific PCR: 5′-CTG AGA AGT TGT GCC CGG-3′

3′-primer for species specific PCR: 5′-GTA GTC CCG CCT GAC CTG-3′

4.1.1.3. Agarose gel electrophoresis and detection of PCR products

After completion of PCR reaction, mix 5 μL of the PCR amplification reaction solution with an appropriate volume of gel loading buffer solution, add the mixture to the wells of 2 w/v% agarose gel, and then perform electrophoresis using 1-fold TAE buffer solution (refer to General Information, Rapid Identification of Microorganisms Based on Molecular Biological Method). Carry out the electrophoresis together with an appropriate DNA molecular marker. Electrophoresis is terminated when the bromophenol blue

dye in the gel loading buffer has moved about 2 cm from the well.

Stain the gel after electrophoresis when not using gel stained in advance with ethidium bromide. Place the gel that has undergone electrophoresis and staining in a gel image analyzer, irradiate with ultraviolet light (312 nm), and confirm its electrophoresis pattern. Compare this to the DNA molecular marker and determine the absence or presence of the target amplification band.

4.2. Judgment

Confirm at first that a 250 bp band is found with the reaction solution to which the positive control primer pair has been added, and confirm there are no bands other than the primer dimer (about 40 bp) in a solution with no sample DNA solution. Next, if a 200 bp band is confirmed when the species specific primer pair is added, the sample is judged to be contaminated with *Peucedanum ledebourielloides* and it is rejected. The sample is judged not to be contaminated with *Peucedanum ledebourielloides* and the purity test is acceptable if a 250 bp band is confirmed with the positive control primer pair, bands are not observed in reaction solution without DNA sample solution, and a 200 bp band is not observed with the species specific primer pair. If a band is not observed with the positive control primer pair, it is to be concluded that the DNA extraction failed and the procedure should be started over again from the DNA extraction step. If bands are confirmed in reaction solution without DNA sample solution, it should be assumed that there was an error in the PCR procedure and therefore the procedure should be repeated again from the step 4.1.1.2. PCR.

5. Reference

1) Y. Guo, *et al.*, *J. Nat. Med*. 60, 149-156 (2006).
2) K. Kondo, *et al.*, *J. Jpn. Bot*. 84, 356-359 (2009).
3) T. Maruyama, *et al.*, *Shoyakugaku Zasshi* 64, 96-101 (2010).
4) T. Maruyama, *et al.*, *J. Nat. Med*. in press.
5) JAS analytical test handbook: genetically modified food quality, labeling analysis manual for individual products, ver. 3, I Fundamental procedure 4.4.1 PCR, (September 24, 2012). Incorporated Administrative Agency Food and Agricultural Materials Inspection Center
6) JAS analytical test handbook: genetically modified food quality, labeling analysis manual for individual products, ver. 3, IV Contamination prevention, (September 24, 2012). Food and Agricultural Materials Inspection Center Independent Administrative Organization
7) Notification No. 110, Director of Food Health Department, March 2001; Partial Amendment: Notification No. 0629002, 2.2.1.2, Director of Food Safety Department, June 2006.
8) Notification No. 0629002, 2.1.3.1.1, Director of Food Safety Department, June 2006.

On the Scientific Names of Crude Drugs listed in the JP

Change the following as follows:

Scientific Names used in the JP and Those being used Taxonomically

Crude Drug	Scientific names used in the JP = Scientific names being used taxonomically (Combined notation, Standard form for author or authors)	Family
	Scientific names that are different from those written in JP but identical to them taxonomically or being regarded as identical, and typical subclassified groups belonging to their species. The names marked with "*" are those being written together in JP.	
Amomum Seed シュクシャ	*Amomum villosum* Loureiro var. *xanthioides* T. L. Wu & S. J. Chen = *Amomum villosum* Lour. var. *xanthioides* (Wall. ex Baker) T. L. Wu & S. J. Chen	*Zingiberaceae*
	Amomum xanthioides Wallich = *Amomum xanthioides* Wall. ex Baker	
	Amomum villosum Lour. var. *nanum* H. T. Tsai & S. W. Zhao	
	Amomum villosum Loureiro var. *villosum* = *Amomum villosum* Lour. var. *villosum*	
	Amomum villosum Lour.	
	Amomum longiligulare T. L. Wu	

G8 Water

Quality Control of Water for Pharmaceutical Use

Change the 4.4.2. Media Growth Promotion Test as follows:

4.4.2. Media Growth Promotion Test

In the media growth promotion test with the R2A Agar Medium, use test strains listed below or other test strains considered equivalent to these test strains.

Methylobacterium extorquens: NBRC 15911

Pseudomonas fluorescens: NBRC 15842, ATCC 17386, etc.

Prior to the test, inoculate these test strains into sterile purified water and starve them at 20 – 25°C for 3 days.

Dilute the fluid containing the test strain starved with sterile purified water to prepare microbial suspensions. When inoculating the R2A Agar Medium with the micro-organisms ($5 \times 10^1 - 2 \times 10^2$ CFU) and incubating at 20 – 25°C for 4 – 7 days, sufficient proliferation of the inoculated strains must be observed.

In the media growth promotion test with the Standard Agar Medium, use test strains listed below or other test strains considered equivalent to these test strains.

Staphylococcus aureus: ATCC 6538, NCIMB 9518, CIP 4.83 or NBRC 13276

Pseudomonas aeruginosa: ATCC 9027, NCIMB 8626, CIP 82.118 or NBRC 13275

Escherichia coli: ATCC 8739, NCIMB 8545, CIP 53.126 or NBRC 3972

Prepare microbial suspensions containing the test strains according to the procedure prescribed in the Microbiological Examination of Non-sterile Products ⟨*4.05*⟩. When inoculating the Standard Agar Medium with a small number (not more than 100 CFU) of the micro-organisms and incubating at 30 – 35°C for 48 hours, sufficient proliferation of the inoculated strains must be observed.

G10 Others

Change as follows:

Basic Concepts for Quality Assurance of Drug Substances and Drug Products

Introduction

Quality of drug substances and products are generally assured through manufacturing and testing under appropriate Good Manufacturing Practice (GMP) conditions reflecting knowledge obtained from designing and developmental stages and manufacturing stage on management of raw materials and other materials, control of manufacturing process, specifications, etc. As shown in the General Notice 5, JP listed drugs are to be tested according to the provisions given in the pertinent monographs, General Notices, General Rules for Crude Drugs, General Rules for Preparations, and General Tests for their conformity to the *Japanese Pharmacopoeia*. In addition to these, compliance with GMP, management of raw materials and other materials, and management of manufacturing process are fundamental factors required to assure the quality of JP listed products in actual production.

The present chapter summarizes general concepts concerning measures for quality assurance of drug substances and products mainly aimed at chemicals, including chemically synthesized antibiotics and semisynthetic antibiotics, synthetic peptides, oligonucleotides, and biotechnological/biological products, and shows the principle idea of quality assurance in the process listing a drug as an individual monograph in the JP. Although radiopharmaceuticals, crude drugs, herbal products, and crude products of animal or plant origin are excluded from the subjects of the concepts, these concepts are useful for the management of any type of drugs.

Basic Concept

In recent years, the mainstream concept for quality control of drugs has been implemented according to a control strategy that their quality is assured by control of manufacturing process, including management of raw material and other materials, and quality testing of final products (drug substances or drug products) that are conducted mutually complementary. The control strategy is implemented based on Quality Risk Management (QRM). The first and most important step is identifying Critical Quality Attributes (CQAs) which are the attributes or properties required to ensure the desired product quality, and it is necessary to specify physical, chemical, biological, microbiological characteristics or properties of the product which should be within the appropriate limits, ranges and distributions. The next step is to guarantee that the CQA falls within the defined range, limit, and distribution by using specification tests, in-process tests and various measures, for that the quality of the drug will eventually be realized.

The Specification is one of the elements of control strategy and not all the CQA need to be included in the specifications. CQA is (1) included in specifications and confirmed by testing final products (including periodical or skip testing, described later), (2) included in specifications and confirmed by process controls (e.g., real time release testing, described later), or (3) not included in specifications but can be ensured by controlling starting materials, raw materials and manufacturing process. As an example of (3), effective control over robust manufacturing processes can assure that certain impurities are controlled at an acceptable risk level or are efficiently removed below an acceptable level, and sometimes the purity testing for the final product may not

be required and omitted from specifications. However, in the case of a drug listed in the JP monograph, regarding the manufacturing process control related to CQA, if necessary, the control method and control value are indicated in the Manufacture in individual monograph.

What kind of control strategy should be applied to a certain CQA is individually determined by QRM according to the understanding and risk of the manufacturing process.

1. Management of manufacturing process

1.1. Considerations of manufacturing process

Adequate design of manufacturing processes and knowledge of their capacity are important to establish manufacturing processes yielding drug substances or drug products that meet specifications and fulfill CQA, and to perform consistent manufacturing control, quality control, etc. appropriately.

From this standpoint, the limits for control of manufacturing processes should be based on information obtained from the entire process spanning the period from the early development through commercial scale production. The appropriateness of the limits also need to be confirmed by evaluation, verification, review, and other examinations of manufacturing processes based on QRM.

In-process tests are tests that may be performed during the manufacture of either the drug substance or drug product, rather than specification tests for the final product. In-process tests are performed for quality verification during manufacturing processes that are likely to influence drug substance or drug product quality, or for confirmation of proper functioning of the manufacturing process. In-process tests may also be used for the evaluation of CQA.

Usually an in-process test is properly designed according to the risk on quality, however, the use of internal action limits by the manufacturer to assess the consistency of the process at less critical steps is also important. Provisional action limits should be set for the manufacturing process based on data obtained during development of the drug and during evaluation and verification of the manufacturing process, and should be further refined based on additional manufacturing experience and data accumulated after product approval for marketing.

1.2. Considerations of raw materials and other materials (starting materials, excipients, packaging materials, etc.)

The raw materials and other materials used in the production of drug substances (or drug products) should meet quality standards, appropriate for their intended use, and appropriate setting of specifications and test methods assuring CQA are required. Especially, biological raw/source materials may require careful evaluation to establish the presence or the absence of deleterious endogenous or adventitious agents. Procedures that make use of affinity chromatography (for example, employing monoclonal antibodies), should be accompanied by appropriate risk management to ensure that such process-related impurities or potential contaminants arising from their production and use do not compromise the quality and safety of the drug substance or drug product.

The quality of the excipients used in the drug product formulation (and in some cases, in the production of drug substance), as well as the primary packaging materials, should be controlled with specifications established based on the characteristics of the drug. If specifications and test procedures for a material are described by the JP, as a rule, at least the JP criteria should be satisfied. Concerning excipients and other materials not listed in the JP, appropriate specifications and test procedures should be established individually.

2. Quality tests of products (specifications)

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. Specifications and test methods of the JP monograph are defined sets of quality characteristics needed for determination of whether the use of a drug substance or a drug product is appropriate for the intended purpose. ''Conformance to the specifications of the JP monograph'' means that the JP-listed drug substances and drug products, when tested according to the procedures described in general tests and drug monographs, will meet the all acceptance criteria except criteria of ''Description'', ''Containers and storage (for drug products)'' and ''Shelf life'' in the JP monographs.

However, as described in ''Basic Concept'' specifications of monographs and test procedures for drug substance and drug product are one part of a total control strategy for assurance of the quality and consistency of the substances/products. Other parts of control strategies include thorough characterization of the drug in developmental stage (specifications and test procedures are established based on the characterization), and management of manufacturing process and products' quality, such as evaluation, verification and review of manufacturing process, and management of raw materials, other materials and manufacturing process, that is to say, compliance with the GMP.

3. Periodic or Skip Testing

Periodic or skip testing is the performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still must meet all acceptance criteria established for that product. This concept may be applicable to, for example, residual solvents and microbiological testing for solid oral dosage forms. It is recognized that only limited data may be available at the time of submission of an application for marketing approval. Implementation of this concept should therefore generally be considered post-approval. When tested, any failure to meet acceptance criteria established for the periodic test should be handled by proper notification of the appropriate regulatory authorities. If these data demonstrate a need of testing for all lots, then batch-by-batch release testing should be reinstated.

4. Real-time release testing (RTRT) and parametric release

RTRT is a type of tests to evaluate the quality of in-

process or final products based on process data (including results of in-process testing and data on process parameters) and to assure that the quality is acceptable. RTRT is a kind of specifications and consists of a valid combination of materials attribute (intermediate products) pre-evaluated and process control. RTRT is used for judgement of products release instead of the release testing of final products when the application containing RTRT is approved by a regulatory authority.

The usage of RTRT does not mean unnecessity of setting tests of a final product directly. Even if the decision of release is made by RTRT, the tests for final products need to be set as specifications. It is because final product testing may be requested for some reasons such as failure of data acquisition due to troubles of equipments used for RTRT and evaluation of stability of final products. The final products, of course, need to meet their specifications, when tested.

Likewise, in the case that the drugs that was approved for marketing with the RTRT is listed in the JP monograph, the RTRT can be continued to use for release judgement. However specification and test procedure that assure the quality as same as the RTRT for final products should be set in the monograph. Even for drugs whose specifications are listed in the monographs, when a new application (or application for partial change) containing RTRT is approved by the regulatory authority, the products release can be judged based on the results of the RTRT instead of the tests prescribed in the monograph. In addition, it is necessary to comply with the specification in the case of conducting the compendial tests. In either case, it is unnecessary to set specification for RTRT in ''Manufacture'' of the monograph since the control criteria for the target CQA is already shown for the RTRT.

If RTRT results fail or trend toward failure, RTRT should not easily be substituted by final product testing. In this case, it is important to investigate the cause properly and need to take corrective action. Also, if RTRT results fail, the products cannot be released unless they were caused by analysis failure such as equipment failure. If RTRT results are trending toward failure, the products release should be made carefully based on the results of the investigation.

Parametric release can be considered a type of real time release. One example of parametric release is to determine the suitability for release of terminally sterilized drug products based on the data on sterilizing process instead of the results of sterility testing. In this case, the release of each batch is based on satisfactory results from monitoring specific parameters, e.g., temperature, pressure, and time during the terminal sterilization phase(s) of drug product manufacturing. Parametric release based on above parameters is more reliable in predicting sterility assurance than is determination of suitability for release based on sterility testing using limited number of final products. Besides, even if parametric release is applied, the final product testing need to be set because the testing is necessary in stability testing and post-marketing surveillance. If in-process data used for parametric release are not acceptable, the products cannot be released. The parametric release differs from RTRT in the case, for example where the data of monitoring specific parameters in terminally sterilized process is failed to obtain by a certain reason such as analysis failure by equipment failure and so on. The incomplete data acquisition means no assurance on sterilization process, it is impossible to substitute parametric release by sterility testing of final products in principle.

Add the following:

Concept on Impurities in Chemically synthesized Drug Substances and Drug Products

1. Classification of impurities found in chemically synthesized pharmaceuticals and the guidance to comply with for their control

Impurities found in chemically synthesized pharmaceuticals are roughly classified into organic impurities, inorganic impurities and residual solvents. Those impurities in the new drug substances and the products are controlled by the following guidelines agreed upon at the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (hereinafter referred to as ''ICH''). More specifically, ''Impurities in New Drugs Substances (PAB/PCD Notification No. 877 dated September 25, 1995)'' (hereinafter referred to as ''ICH Q3A Guideline'')[1] on specifications for organic impurities in drug substances applies to applications for marketing approval after April 1, 1997, while ''Impurities in New Drug Products (PAB/PCD Notification No. 539 dated June 23, 1997'' (hereinafter referred to as ''ICH Q3B Guideline'')[2] on specifications for organic impurities in drug products applies to applications for marketing approval after April 1, 1999. Meanwhile, specifications for inorganic impurities were specified by Japanese pharmacopoeial standards and known safety data. Now ''Guidelines for Elemental Impurities (PFSB/ELD Notification No. 4 dated September 30, 2015)'' apply to applications for marketing approval after April 1, 2017. In regard to residual solvents, ''Impurities: Guidelines for Residual Solvents (PAB/ELD Notification No. 307 dated March 30, 1998)'' (hereinafter referred to as ''ICH Q3C Guideline'') applies to applications for marketing approval after April 1, 2000. Especially in regard to DNA-reactive impurities, ''Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (PSEHB/ELD Notification No. 3 dated November 10, 2015)'' applies to applications for marketing approval after January 15, 2016. Although ICH Q3A guideline does not cover optical enantiomers, a type of organic impurities, ''Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (PMSB/ELD Notification No. 568 dated May 1, 2001)'' (hereinafter referred to as ''ICH Q6A Guideline''), which was published subse-

quently, provides that enantiomers are impurities that should be controlled and, if measurable, should be controlled in accordance with the principle of the ICH Q3A guideline.

Control of impurities in accordance with the guidelines mentioned above is expected also for pharmaceuticals other than new drug substances and new drug products. Their applications for marketing (or applications for partial changes) are subject to those guidelines when necessary. The General Notices of the JP 17th Edition states that residual solvents of all JP-listed drugs, in principle, have to be controlled in accordance with specification ''Residual Solvents'' in General Tests unless otherwise specified in the individual monograph. In regard to elemental impurities, it has been decided in the basic principles for the preparation of the JP 18th Edition to create a roadmap for their incorporation into the JP for listing and to address its implementation.

2. The concept of ICH Q3A and Q3B guidelines for the control of organic impurities

ICH Q3A and Q3B guidelines require setting acceptance criteria for organic impurities based on the information gained from development stages for new drugs. Concerning impurities in drug substances, ICH Q3A guideline refers to the items to be examined from chemical and safety perspectives. ICH Q3B guideline complements Q3A guideline, and have the same basic concept as Q3A. Chemical aspects to be examined include classification and identification of impurities, their reporting method, specification settings and analytical methods. Safety aspects include specific guidelines for qualifying the safety of impurities that were not present, or were present at substantially lower levels, in batches of a drug substance used in safety and clinical studies.

Qualification of the safety is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should describe a rationale for establishing impurity acceptance criteria that includes safety considerations in attachments when applicated for approval. The level of any impurities present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified.

Identified impurities, unidentified impurities and total impurities are specified based on the data obtained according to the guidelines. The threshold of unspecified impurities in a drug substance is determined depending on the daily intake of the drug substance. When the maximum daily dosage is not more than 2 g, it is set at 0.10%. The establishment of individual specifications is required for impurities at a level greater than 0.10%.

In regard to drug products, the ICH Q3B guideline cover the degradation products of drug substances or reaction products between the drug substance and additive/primary packaging. Therefore, even if organic impurities other than degradation products (e.g., by-products and synthetic intermediates) in the drug substance are found as impurities in the drug product, they need not be monitored or specified since they have already been controlled as the drug substance specifications. However, degradation products elevated in the drug product need to be monitored and specified.

3. Principles for controlling organic impurities in the articles listed in the JP

Conventionally in the JP, specified impurities, unspecified impurities and total impurities are specified in accordance with ICH Q3A and Q3B guidelines for pharmaceutical products, whose impurities have been controlled by those guidelines, in the process listing in the JP. (However, this shall not apply to the long-term listed pharmaceutical products which had existed in the JP before these guidelines were applicable. However, when a new application is filed for those JP-listed pharmaceutical products, control of impurities in accordance with ICH Q3A and Q3B guidelines may be required, if necessary.) In order to specify the impurities, analysis data during development submitted from the drafting company and impurity analysis data from commercial production batches after consistent manufacturing is achieved should be assessed. Safety evaluation is not required again for the process listing in the JP since it has been performed at the time of approval.

ICH Q3A and Q3B guidelines cover impurities in the drug substances manufactured by chemical syntheses and the drug products manufactured with those drug substances. Similarly, the following types of products are not covered in the JP: biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semi-synthetic products derived therefrom, herbal products and crude products of animal or plant origin.

When organic impurities assessed in accordance with the principles of ICH Q3A and Q3B guidelines are listed as JP tests of purity, the operational rationality of the JP is considered and its own modification is added. (i) Except in exceptional circumstances, impurity reference standards are not established. In order to identify an impurity using liquid chromatography, the relative retention time of the impurity to the drug substance is used for identification. (ii) When only unidentified impurities in highly pure pharmaceutical products (not more than 0.1%) are specified, it is generally exempted to set acceptance criteria for total impurities. (iii) When acceptance criteria set based only on actual measured values result in many impurities with slightly different acceptance criteria, consideration can be given so that the purity test consists of a small number of representative acceptance criteria, if possible. (iv) Chemical structural information and the chemical name of the impurities are not disclosed. Those measures enable impurity control without impurity reference standards, and can simplify system suitability test for highly pure pharmaceutical products.

Meanwhile, the method to identify impurities by use of relative retention time is column-dependent and analysis becomes difficult when appropriate columns are not available. Therefore, the JP 17th Edition also allows the use of the analysis method with impurity reference standards when designing purity tests for a drug substance. In addition, the

JP adopted a policy to disclose chemical names and structure formulas as the information on impurities including, in principle, optical enantiomers.

The JP-specific consideration may be given to purity tests for organic impurities in drug products in the process listing in the JP. Also in the JP, impurities derived from the products of the reaction between the drug substance and additive/primary packaging are specified as impurities in the drug product. Those impurities are formulation-dependent and may not be formed in different formulations. Since the JP is an official compendium that allows a wide variety of formulations, when it is not appropriate to specify impurities uniformly in the individual monograph, they are subject to the specifications at the time of approval, along with the statement ''Being specified separately when the drug is granted approval based on the Law.''

When the specifications for impurities are reviewed for a new entry of a pharmaceutical product in an individual monograph of the JP, acceptance criteria for impurities may be included in the review according to the following concepts. ICH Q6A guideline point out: Data available upon the marketing application are limited and it has to be taken into consideration that the limited data may influence the design of acceptance criteria. Regarding impurities, since impurity profiles gained during the manufacturing stages may sometimes be different from that gained from development stage, it is stated that changes in impurity profiles at the manufacturing stage should be considered as appropriate. According to this concept, for impurities which should be specified in the process listing in the JP, not only information from development stage but also information about impurity profiles if there are changes at the manufacturing stage, and information at the stage after the product manufacturing becomes stable (hereinafter referred to as the ''stable production stage'') should be taken into consideration.

However, it is undesirable to remove impurities that are present at substantially lower levels, or become undetectable at the stable production stage indiscriminately from the list of candidate compounds to be specified. JP-listed drugs are accepted as drugs by conformance to the specifications in the individual monograph. However, generic drugs, whose manufacturing methods are not necessarily the same as that of the drug substance used for JP monograph, may have different impurity profiles and contain such impurities. Providing information in the process listing in the JP based on the detection results during development stage may result in encompassing impurities found in drug substances and drug products distributed as JP drugs.

Therefore, before the removal of impurities that are present at substantially lower levels or become undetectable at the stable production stage from the JP specification list, the need to establish specifications should be fully examined based on ICH Q3A and Q3B guidelines with respect to safety.

For a drug substance that was approved by the method to identify its impurities with impurity reference materials, it is desirable also in the individual JP monograph, in principle, to establish specifications and test methods appropriately so that the specified impurity becomes identifiable. In regard to impurity control during the manufacturing process, impurities can be controlled by establishing an appropriate control strategy including release testing, in-process tests and process parameters control.

References

1) ICH:Harmonised Tripartite Guideline, Impurities in New Drug Substances.
2) ICH:Harmonised Tripartite Guideline, Impurities in New Drug Products.

Add the following:

Glossary for Quality by Design (QbD), Quality Risk Management (QRM) and Pharmaceutical Quality System (PQS)

1. Introduction

The purpose of this glossary is to define terms, used for developing the new concept of quality assurance in ICH Q8-11 guidelines so-called Q quartet, and to explain the concept. The terms shown here are determined as the result of discussion for long time in ICH, and are most important to understand the concept of systematic quality assurance based on science and quality risk management, as shown by the guidelines. The usage may not necessarily accord with general usage, however it is necessary to keep in mind that the following definition is used in the regulatory application of pharmaceuticals. The terms used in ICH Q8 to Q11 are shown below in their order. For terms explained in more than one guideline, the name of duplicated guideline is described in parentheses at the end of the corresponding sentence.

2. Glossary

[ICH Q8 Guideline]

Control Strategy: A planned set of controls, derived from current product and process understanding, that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10, Q11). A control strategy is expected irrespective of development approaches. Under the development approach using Quality by Design, testing, monitoring or controlling can be shifted earlier into the process.

Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. Process validation protocol can use Continuous Process Verification (CPV) to the process validation protocol for the initial and ongoing commercial production (ICH Q11). Generally, for initial process validation, CPV is more appropriate when QbD approach has been applied. However, it can also be used when extensive process knowledge has been gained through commercial manufacturing experience.

Process Robustness: Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality (ICH Q11).

Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q11). For example, CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability as described in ICH Q8, however it is usual to include product purity and strength itself in CQAs.

Formal Experimental Design: A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as ''Design of Experiments'' (DoE). The factors to be studied in a DoE could come from the risk assessment exercise or prior knowledge.

Design Space (DS): The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q10, Q11). Design space can be updated over the lifecycle as additional knowledge is gained. Since Proven Acceptable Range (PAR) from only univariate experimentation may lack an understanding of interactions between process parameters and/or material attributes, it should be noted that a combination of PAR does not constitute a design space.

Quality: The degree to which a set of inherent properties of a product, system or process fulfills requirements (ICH Q6A, Q8, Q10). The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity (ICH Q6A, Q8, Q9, Q10).

Process Analytical Technology (PAT): A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Quality Target Product Profile (QTPP): A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. Quality Target Product Profile describes the design criteria for the product, and should therefore form the basis for development of the product (ICH Q8).

Lifecycle: All phases in the life of a product from the initial development through marketing until the product's discontinuation (ICH Q11).

Real Time Release Testing (RTRT): The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls (ICHQ11). Parametric release is one type of Real Time Release Testing. It is based on process data rather than testing of material and/or a sample for a specific attribute. For details, refer to ''Basic Concepts for Quality Assurance of Drug Substances and Drug Products'' in General Information.

Proven Acceptable Range (PAR): A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.

[ICH Q9 Guideline]

Decision Maker(s): Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.

Harm: Damage to health, including the damage that can occur from loss of product quality or availability.

Trend: A statistical term referring to the direction or rate of change of a variable(s).

Detectability: The ability to discover or determine the existence, presence, or fact of a hazard.

Severity: A measure of the possible consequences of a hazard.

Product Lifecycle: All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Hazard: The potential source of harm (ISO/IEC Guide 51).

Quality System: The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirements: The explicit or implicit needs or expectations of the patients or their surrogates (e.g., health care professionals, regulators and legislators). In this document (ICH Q9), ''requirements'' refers not only to statutory, legisla-

tive, or regulatory requirements, but also to such needs and expectations.

Stakeholder: Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

Risk: The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk Communication: The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk Control: Actions implementing risk management decisions (ISO Guide 73).

Risk Acceptance: The decision to accept risk (ISO Guide 73).

Risk Reduction: Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk Identification: The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Risk Evaluation: The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk Analysis: The estimation of the risk associated with the identified hazards.

Risk Management: The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.

Risk Review: Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

[ICH Q10 Guideline]

Innovation: The introduction of new technologies or methodologies.

Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regard to quality (ICH Q10 based upon ISO 9000:2005) .

Outsourced Activities: Activities conducted by a contract acceptor under a written agreement with a contract giver.

State of Control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

Performance Indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as ''performance metrics'' in some regions.

Continual Improvement: Recurring activity to increase the ability to fulfil requirements (ISO 9000:2005).

Senior Management: Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site (ICH Q10 based in part on ISO 9000:2005).

Capability of a Process: Ability of a process to realize a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms (ISO 9000:2005).

Product Realization: Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorization) and internal customers requirements.

Corrective Action: Action to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence (ISO 9000:2005).

Enabler: A tool or process which provides the means to achieve an objective.

Knowledge Management: Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components.

Quality Planning: Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives (ISO 9000:2005).

Quality Policy: Overall intentions and direction of an organization related to quality as formally expressed by senior management (ISO 9000:2005).

Quality Manual: Document specifying the quality management system of an organization (ISO 9000:2005).

Quality Objectives: A means to translate the quality policy and strategies into measurable activities.

Quality Risk Management (QRM): A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle (ICH Q9, Q10). For details, refer to ''Basic Concept of Quality Risk Management'' in General Information.

Feedback/Feedforward: The modification or control of a process or system by its results or effects. Feedback/feedforward can be applied technically in process control strategies and conceptually in quality management. Feedback is to

reflect results to a previous process (for example: a control of the supply of materials in a previous process), and feed-forward is to reflect results to a subsequent process (for example: a control of time for drying in a subsequent process).

Change Management: A systematic approach to proposing, evaluating, approving, implementing and reviewing changes.

Preventive Action: Action to eliminate the cause of a potential non-conformity or other undesirable potential situation. NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence (ISO 9000:2005).

[ICH Q11 Guideline]

Chemical Transformation Step: For Chemical Entities, a step involved in the synthesis of the chemical structure of the drug substance from precursor molecular fragments. Typically it involves C—X or C—C bond formation or breaking.

Contaminants: Any adventitiously introduced materials (e.g., chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of the drug substance or drug product (ICH Q6B).

3. References

1) ICH: Guideline for Q8(R2), Pharmaceutical Development.
2) ICH: Guideline for Q9, Quality Risk Management.
3) ICH: Guideline for Q10, Pharmaceutical Quality Systems.
4) ICH: Guideline for Q11, Development and Manufacture of Drug Substance (Chemical Entities and Biotechnological/Biological Entities).
5) ICH: Quality Implementation Working Group, Points to Consider (R2), ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation
6) ICH: Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4)

International Harmonization Implemented in the Japanese Pharmacopoeia Seventeenth Edition

Add the following:

Sep. 2017

Harmonized items	JP 17 (Supplement II)	Remarks
Conductivity	**2.51 Conductivity Measurement**	
Introduction	(Introduction)	
Apparatus	1. Apparatus	
Cell constant determination	2. Cell constant determination	
Calibration of temperature	3. Calibration of temperature	
Calibration of measurement electronics	4. Calibration of measurement electronics	
Temperature compensation	5. Temperature compensation	Deletion of ISO and examples of individual monograph.
Conductivity measurement of fluids	6. Conductivity measurement of fluids	
JP's particular description: 5. Temperature compensation; Additional explanation for non-linear temperature compensation data.		

Feb. 2002/Oct.2009 (Rev. 1)/May 2016 (Rev. 2)

Harmonized items	JP 17 (Supplement II)	Remarks
Ethylcellulose	**Ethylcellulose**	
Definition	origin, limits of content	
	Description	Non-harmonized item
Identification IR	Identification	
Acidity/alkalinity	Purity (1) Acidity or alkalinity	
Viscosity	Viscosity	
Acetaldehyde	Purity (4) Acetaldehyde	
Chlorides	Purity (2) Chloride	
Loss on drying	Loss on drying	
Sulfated ash	Residue on ignition	
Assay	Assay	
Labelling	labelling	Not specified for the name and concentration of antioxidant in labelling
	Containers and storage	Non-harmonized item
JP's particular description: Purity Heavy metals.		

July 2016

Harmonized items	JP 17 (Supplement II)	Remarks
Hydroxyethylcellulose	**Hydroxyethylcellulose**	
Definition	origin, limits of content	
	labeling of viscosity	Non-harmonized item
	Description	Non-harmonized item
Identification A (IR)	Identification (1)	
Identification B	Identification (2)	
	Viscosity	Non-harmonized item
pH	pH	
Chlorides	Purity (1) Chloride	
Nitrates	Purity (2) Nitrate	
Aldehydes	Purity (4) Aldehydes	
Loss on drying	Loss on drying	
Sulfated ash	Residue on ignition	
Assay	Assay	
	Containers and storage	Non-harmonized item
JP's particular description: Purity (3) Heavy metals.		

Change the following as follows:

Nov. 2016 (Corr. 1)

Harmonized items	JP 17 (Supplement II)	Remarks
Isomalt	**Isomalt Hydrate**	
Definition	origin, limits of content	
	Description	Non-harmonized item
Identification	Identification (2)	
Conductivity	Conductivity	
Reducing sugars	Purity (4) Reducing sugars	
Related substances	Purity (3) Related substances	
Nickel	Purity (2) Nickel	
Water	Water	
Assay	Assay	
Labelling	labelling	
	Containers and storage	Non-harmonized item
JP's particular description: Identification (1) Color reaction; Purity (1) Heavy metals; Purity (3) Related substances Test for required detectability, System repeatability; Assay System repeatability.		

Sep. 2017 (Rev. 2)/Oct. 2018 (Rev. 3)

Harmonized items	JP 17 (Supplement II)	Remarks
Microcrystalline Cellulose	**Microcrystalline Cellulose**	
Definition	origin	
	Description	Non-harmonized item
Identification A (IR)	Identification (2)	
Identification B (wet chemistry)	Identification (1)	
Identification C (degree of polymerization)	Identification (3)	
Conductivity	Conductivity	
pH	pH	
Loss on drying	Loss on drying	
Residue on ignition	Residue on ignition	
Bulk density	Bulk density	
Water-soluble substances	Purity (2) Water-soluble substances	
Ether-soluble substances	Purity (3) Diethyl ether-soluble substances	
Microbial limits	Microbial limits	
	Containers and storage	Non-harmonized item
JP's particular description: Labelling (Mean degree of polymerization and loss on drying value); Identification (3) In the range of label; Purity (1) Heavy metals; Loss on drying In the range of label.		

Sep. 2017 (Rev. 2)

Harmonized items	JP 17 (Supplement II)	Remarks
Hypromellose	**Hypromellose**	
Definition	origin, limits of content	
	Description	Non-harmonized item
Labeling	labeling of viscosity	
Identification (1)	Identification (1)	
Identification (2)	Identification (2)	
Identification (3)	Identification (3)	
Identification (4)	Identification (4)	
Identification (5)	Identification (5)	
Viscosity	Viscosity	
Method 1	Method I	
Method 2	Method II	
pH	pH	
Loss on drying	Loss on drying	
Residue on ignition	Residue on ignition	
Assay	Assay	
	Containers and storage	Non-harmonized item
JP's particular description: Purity Heavy metals.		

Sep. 2017 (Rev. 3)

Harmonized items	JP 17 (Supplement II)	Remarks
Methylcellulose	**Methylcellulose**	
Definition	origin, limits of content	
	Description	Non-harmonized item
Labeling	labeling of viscosity	
Identification (1)	Identification (1)	
Identification (2)	Identification (2)	
Identification (3)	Identification (3)	
Identification (4)	Identification (4)	
Identification (5)	Identification (5)	
Viscosity	Viscosity	
Method 1	Method I	
Method 2	Method II	
pH	pH	
Loss on drying	Loss on drying	
Residue on ignition	Residue on ignition	
Assay	Assay	
	Containers and storage	Non-harmonized item
JP's particular description: Purity Heavy metals.		

Sep. 2017 (Rev. 2)

Harmonized items	JP 17 (Supplement II)	Remarks
Anhydrous Dibasic Calcium Phosphate	**Anhydrous Dibasic Calcium Phosphate**	
Definition	limits of content	
	Description	Non-harmonized item
Identification (1)	Identification (1)	
Identification (2)	Identification (2)	
Acid-insoluble substances	Purity (1) Acid-insoluble substances	
Chloride	Purity (2) Chloride	
Sulfate	Purity (3) Sulfate	
Carbonate	Purity (4) Carbonate	
Barium	Purity (6) Barium	
	Purity (7) Arsenic	Non-harmonized item
Loss on ignition	Loss on ignition	
Assay	Assay	
	Containers and storage	Non-harmonized item
JP's particular description: Purity (5) Heavy metals.		

Delete the following:

Saccharin
Saccharin Sodium Hydrate
Total Protein Assay

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