Guideline for Drafting Monographs for The Japanese Pharmacopoeia, Nineteenth Edition (Partial revision) (Tentative translation version*)

April 2023

Office of Review Management
Pharmaceuticals and Medical Devices Agency

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Contents

Preface

Pursuant to Article 41 of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Law No. 145, 1960, hereinafter referred to as the “Law”), the Japanese Pharmacopoeia (JP) is established in order to properly assure the quality of the medicines, and has been widely utilized by many peoples involved in the pharmaceutical fields of administration, industry, medical care, research, education, and so on. In the “Basic Principle for the preparation of the Japanese Pharmacopoeia, Nineteenth Edition”, which was issued by the Ministry of Health, Labour and Welfare (MHLW) (as the office notice of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, October 25, 2021), the JP is defined as “an official compendium that defines the specifications, criteria and the standard test methods necessary to properly assure the quality of the medicines in Japan”. For playing the role, the JP had a requirement of the entire revision at least once every 10 years, and since the Ninth Edition (1976) the revision had been made every 5 years. And, since the Twelfth Edition (1991) a supplement has been promulgated twice in the course of the entire revision. Since April 2004 the Pharmaceuticals and Medical Devices Agency (PMDA) is taking on the management of the organization of JP discussion committees as the secretariat to reinforce the JP head office commissioned by MHLW, except the committee on JP managed by the Pharmaceutical Affairs and Food Sanitation Council.

PMDA has established 16 committees of each field for preparation of JP, and they are processing the deliberation of the submitted drafts from the pharmaceutical manufacturers etc. In order to increase the degree of completion of the drafts being submitted, to promote the deliberations and to achieve the integrity of the JP, PMDA established and published this Guideline. The 18th Edition of the JP was notified (or promulgated) in June 2021, and “Basic Principle for drafting the Japanese Pharmacopoeia, Nineteenth Edition” was issued by MHLW on October 25, 2021. The "Guideline for Drafting Monographs for the Japanese Pharmacopoeia Nineteenth Edition" was published in March 2022 so that it could be applied to the partial revisions (including Supplement I published in December 2022) of the current Eighteenth Edition planned in near future. Recently, in response to the agreement on the harmonization of Chromatography at the Pharmacopeial Discussion Group Meeting, 2.00 Chromatography was included in the General Tests, Processes and Apparatus (hereinafter referred to as the “General Tests”) of the Supplement I to the Japanese Pharmacopoeia Eighteenth Edition. We have decided to partially revise "Guideline for Drafting Monographs of the Japanese Pharmacopoeia Nineteenth Edition" by adding consideration when describing about chromatography and reviewing other descriptions.

We are happy if this guideline is utilized by all of you involved in the pharmaceutical fields of administration, industry, medical care, research, education and so on with the respective scene. The guideline will be revised appropriately when the necessity for revision arises according to the progress of science and the medical demand.

We are very grateful to the members of the General Subcommittee for the Japanese Pharmacopoeia Draft Review Committee chaired by Dr. Yukihiro Goda, Director General Emeritus, National Institute of Health Sciences for their tremendous efforts for preparing this guideline.

Director, Office of Review Management
Pharmaceuticals and Medical Devices Agency
April 2023

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(March 2023)

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1. Purpose

The purpose of this guideline is to improve the completeness of "draft monographs" for The Japanese Pharmacopoeia, Nineteenth Edition (hereinafter, JP19), to facilitate the deliberation in the committee, and to keep consistency of the description across JP by specifying items necessary for the preparation of JP19, such as concrete methods of preparation and description of "draft monographs".

2. Content

This guideline is consisted of "Part 1 Detailed rules for preparing a draft monograph for JP19" and "Part 2 Submission Documents for a Draft Monograph".

"Part 1 Detailed rules for preparing a draft monograph for JP19" provides specific guidance and methods for creating draft monographs on the revision of JP.

"Part 2 Submission Documents for a Draft Monograph" provides guidance, including precautions, for preparations and submission of draft monographs by using specific templates.

3. Scope

The scope of this guideline is "drug substances and their preparations in Official Monographs".

For any matters not covered by this guideline, specific descriptions can be adopted depending on the particularity of the monograph concerned.

This guideline is also applied, to the extent possible, to the description of the General Tests.

4. Application

This guideline is primarily applied to JP19; however, its principles are also applied to a partial revision (including supplements) planned for the current Eighteenth Edition in the future.

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Part 1 Detailed rules for preparing a draft monograph for JP19

1. Basic items

1.1 Establishment of the specifications and test procedure

1.1.1 Selection of test items

As provided in the Article 41 of the Act, the purpose of the JP is to ensure properly description and quality of the drug products, and therefore establishes specific test items necessary to comprehensively secure a certain level of consistent quality of the drugs that can be considered equivalent in terms of efficacy and safety. However, if there is a rational reason to believe appropriate quality of a drug can be ensured based on its raw materials, manufacturing processes, etc., it is not necessary to establish all items specified in **3.1**.

1.1.2 Setting specification values/acceptance criteria

High purity or content are not necessarily required as specification values/acceptance criteria, and the limits, acceptable ranges and other appropriate standards of the drug necessary to assure a certain level of quality should be specified based on the actual measurement values and the results from safety studies, stability test results (such as long-term stability), etc. as necessary, in order to ensure the efficacy and safety of the drug. However, in cases where it is extremely difficult to set uniform specification values required for ensuring a certain level of quality in process-related impurities of biologicals, as well as dissolution, osmotic pressure ratio, pH, etc. of preparations due to the difference in manufacturing processes even for the same product, it is not necessary to set specification values/acceptance criteria even though test items are listed. Instead, such specification values or acceptance criteria can be set during the regulatory approval process based on the Law. In addition, even when using the specification values/acceptance criteria described in the Japanese Pharmaceutical Codex (hereinafter, JPC), it is preferable to propose specification values/acceptance criteria considering the actual measurement values, as standards are examined based on these submitted actual measurement values.

1.1.3 Establishment of the test procedure

Establish a test procedure which effectively ascertains the quality of the drugs clearly. It is not necessary to describe the test procedure in the test item in the case the specification values/acceptance criteria are set during approval process by the Law.

For the test procedure, consider simplifying it so far as it attains the necessary purposes. Furthermore, consider making the test procedure reasonable by introducing the operating procedure that can be verified for the validity of the testing as required, the operating procedure that can be verified for the sensitivity and precision to meet the intended purpose such as performing the test together with the standard solution, and so on. From these aspects, actively introduce simple and sensitive test methods, such as instrumental analysis for the tests of Identification and Purity, and relative test methods for Assay.

In stipulating the preparation method for a test sample, make efforts to reduce as far as possible the amount of the sample and the reagents used in the test.

1.1.4 Definition of "Being specified separately including the case when the specification is granted approval based on the Law"

Establish the required test items and specifications/acceptance criteria when drafting the monograph.

However, as shown in **1.1.2**, in cases where it is extremely difficult to set uniform specification values required for ensuring a certain level of quality in process-related impurities of biologicals, as well as dissolution, osmotic pressure ratio, pH, etc. of preparations due to the difference in manufacturing processes even for the same product, and/or in cases where certain aspects of specification should be protected as part of the intellectual property right, it is not necessary to set the specification values/acceptance criteria. Instead, the description "being specified separately when the drug is granted approval based on the Law" (hereinafter this sentence is simplified) is allowed after the deliberation of the Japanese Pharmacopoeia Draft Review Committee.

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"Being specified separately" means that specification values or acceptance criteria is defined separately in the marketing authorization dossier according to the Law. In addition, it also includes cases where it is judged unnecessary to be specified in the approval review based on the Law and hence not specified in the dossier.

1.2 Consideration for hazardous reagents

Make efforts to set the test procedure that has consideration for human and environment impact by not using hazardous reagents and so on.

Avoid using the following reagents or minimize their amounts of use.

- Reagents which are Hazardous and the exposure to the operator is concerned
- Reagents which are Heavy environmental load due to adverse reaction and persistency, etc.
- Reagents which need Special handling (narcotics, stimulants, etc.)

Never use the following reagents, in principle.

- Mercuric compounds
- Cyanides
- Benzene
- Carbon tetrachloride
- 1,2-Dichloroethane
- 1.1-Dichloroethene
- 1,1,1-Trichloroethane
- 1,4-Dioxane

The following reagents can be used in the case where no alternative solvents are available.

- Halogenated compounds (chloroform, dichloromethane, etc. Select preferentially dichloromethane if both are possible to use)
- Carbon disulfide.

2. General matters

2.1 Wording and House Style

Make the description in the JP the colloquial style and the lateral writing.

In principle, use the terms in the following texts:

- *Kanji* in common-use and contemporary Japanese syllabic writing
- Japanese Scientific Terms compiled by Ministry of Education, Culture, Sports, Science and Technology (MEXT)

However, *Kanji* other than *Kanji* in common use can be used for terms very likely to be misunderstood without it.

2.1.1 Style for declensional kana endings and so on

For the declensional kana endings, terms to be written in kana, changes of characters and technical terms, follow the examples of House Style in principle. However, use the following *Kanji*: 顆(in granule), 煎(in decoction), 膏(in ointment), 漿(in blood plasma), 絆(in plaster), 坐(in suppository) and so on.

(*Note: This rule is applied to the Japanese version.*)

2.1.2 Test solution and standard solution

Use "Test Solution" and "Standard Solution" defined in each test or Standard Solution in General Tests.

When these are prepared in each monograph, state these as "the sample solution" and "the standard solution", respectively.

2.1.3 Punctuation marks

Use punctuation marks of [，　], [．　] and [：]. Put them appropriately not to generate any misunderstanding.

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(*Note: This rule is applied to the Japanese version to avoid using* [、] and [。].)

2.1.4 Names of drugs, names of reagents, words of foreign origins, and names of plants and animals

Express the followings in *Katakana* or in *Kanji* in common use, in principle.

- Drug name
- Reagent name

Express the followings in *Katakana*, in principle.

- Word of foreign origin
- Plant name
- Animal name

(*Note: This rule is not applied to the English version except for drug name.*)

2.1.5 Repeating signs

In principle, do not use repeating signs of [々], [ゝ], and [ゞ]. They are, however, allowed to be used in common words [e.g. 各々(each), 徐々に(gradually)].

(*Note: This rule is applied to the Japanese version.*)

2.1.6 Numerical figure

Use Arabic numerals.

If necessary, Roman numerals are allowed to be used, and for idiomatic phrases, Japanese numerical characters are to be used:

[Example] 一般(general), 一次(primary), 一度(once), 一部(part), 一つ(one), 二層(two-layer),四捨五入(rounding), 二酸化イオウ(sulfur dioxide), 二塩酸塩(dihydrochloride), 二グルコン酸塩(digluconate), 三水和物(trihydrate), エチレンジアミン四酢酸二ナトリウム(disodium ethylenediaminetetraacetate), 酸化リン(V)(phosphorus(V) oxide)

(*Note: This rule is not applied to the English version except for Arabic numerals and Roman numerals.*)

2.1.6.1 Expression for large numerical figures

Express the numerical figures consecutively without putting a comma at every three digits.

(*Note: This rule is applied to the Japanese version.*)

2.1.7 Characters and signs

Use characters and signs of the first and the second levels of JIS, in principle.

Write the scientific name of animals, plants or bacteria, and so on, symbols for physical values e.g. refractive index *n*, specific gravity *d*, etc.) or variables in formulae (e.g. absorbance A_1, peak area ratio Q_S, etc.) in italics, in principle.

2.1.7.1 Algebraic expression of variables

The algebraic expression of variables should be as follows:

Mass: *M*
Volume: *V*
Absorbance: *A*
Peak area: *A*
Peak height: *H*
Ratio of peak area, etc.: *Q*
Sum of peak area, etc.: *S*
Labeled amount of preparation unit: *C*

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2.1.8 Use of parentheses

In principle, the order of use of parentheses is as follows.

The order of parenthesis: ({ [( )] })

[Example] 2-{(*Z*)-(2-Aminothiazol-4-yl)-[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfoazetidin-3-ylcarbamoyl]methylene aminooxy}-2-methyl-1-propanoic acid

Amount [mg (potency)] of lysozyme

Amount [μg (potency)] of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$)

In the case of calculating formula, its order is as follows.

The order of parenthesis in calculating formulas: [{ ( ) }]

[Example] Amount (%) of related substances other than the desamido substance = $[\{A_T - (A_I + A_D)\} / A_T] \times 100$

2.2 Specification value/acceptance criterion and actual measurement value

2.2.1 Definition of the specification value and the actual measurement value

The specification value is the standard value for judging the conformities to their Specific Physical and/or Chemical Values, Purity Test, Special Test, and Assay based upon the final test results.

The actual measurement value is the measurement result obtained from a test according to the test procedure described in each of the test items.

2.2.2 Specification value

2.2.2.1 Notation of the specification value

Express the specification value in range, such as "$X – X'$%" and "$Y – Y'$°C", or as "not more than (not less than, less than) Z%".

2.2.2.2 Digit number of the specification value

Taking the digit number of significant figures of an actual measurement value into consideration, determine the digit number of the specification value from the standpoint of assuring a certain level of quality.

If the specification value is 1000 or more and the significant figures need to be identified, the specification value can be described with the exponential.

[Example] 10,000 – 12,000 units → $1.0 \times 10^4 – 1.2 \times 10^4$ units

Not less than 30,000 units → Not less than 3.0×10^4 units

In addition, express the acceptance criterion of the microbial limit as 10^1, 10^2 and 10^3.

[Example] The acceptance criteria of TAMC and TYMC are 10^2 CFU/mL and 10^1 CFU/mL, respectively.

Note —TAMC : Total Aerobic Microbial Count

TYMC : Total Combined Yeasts/Moulds Count

2.2.3 Rounding the actual measurement value

According to the General Notices of the JP, when the specification value or significant figures of the specification value has [n] digit(s), the actual measurement value is obtained up to [n+1] digits and then the number of the [n+1] digit is to be rounded off and make the digit number of [n].

When an actual measurement value is obtained up to the more digits, the numbers of [n+2] digit and the lower are rounded down and the [n+1] digit is to be rounded off in order to make the digit number of [n].

[Example] When the specification value/acceptance criterion or its significant figures is in 2 digits;

1.23 → 1.2, 1.25 → 1.3, 1.249 → 1.2

2.54×10^3 (2,540) → 2.5×10^3 (2,500),

2.56×10^3 (2,560) → 2.6×10^3 (2,600),

2.549×10^3 (2,549) → 2.5×10^3 (2,500)

2.3 Units and their symbols

Physical and chemical units should be coordinated with the SI Unit System in accordance with the indications in the General Notices of the JP. However, the SI Unit System is not required for biological units such as endotoxin units.

The unit of w/v% should be used only for expressing concentration such as formulation or ingredient concentration of preparations.

meter	m
centimeter	cm
millimeter	mm
micrometer	μm
nanometer	nm
kilogram	kg
gram	g
milligram	mg
microgram	μg
nanogram	ng
picogram	pg
mole	mol
millimole	mmol
Celsius degree	°C
square centimeter	cm^2
liter	L
milliliter	mL
microliter	μL
megahertz	MHz
Newton	N
per centimeter	cm^{-1}
kilopascal	kPa
Pascal	Pa
mole per liter	mol/L
millimole per liter	mmol/L
Pascal second	Pa·s
millipascal second	mPa·s
square millimeter per second	mm^2/s
lux	lx
mass per cent	%
mass parts per million	ppm
mass parts per billion	ppb
volume per cent	vol%
volume parts per million	vol ppm
weight per volume per cent	w/v%
microsiemens per centimeter	$\mu S \cdot cm^{-1}$
hydrogen ion exponent	pH
endotoxin unit	EU
colony-forming unit	CFU
radian	rad
degree (angle)	°
osmol	Osm
milliosmol	mOsm
equivalent	Eq
milliequivalent	mEq

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2.4 Temperature

In principle, describe a temperature for testing or storage with a numerical figure, however, the following expression is also acceptable.

2.4.1 Definition related to temperature

2.4.1.1 Definition of terms related to temperature

The terms related to temperature are specified as follows.

"Standard temperature"	20°C
"Ordinary temperature"	15 – 25°C
"Room temperature"	1 – 30°C
"Lukewarm temperature"	30 – 40°C

2.4.1.2 Definition of "Cold place"

"Cold place", unless otherwise specified, is a place where the temperature is between 1°C and 15°C.

2.4.1.3 Definitions of terms related to water temperature

The terms related to water temperature are specified as follows.

"Cold water"	10°C or below
"Lukewarm water"	30 – 40°C
"Warm water"	60 – 70°C
"Hot water"	about 100°C

2.4.1.4 Definitions of "warming" etc.

The term "to warm" generally means to heat at 60 – 70°C.

In addition, when "heating" or "igniting", state the concrete temperature as much as possible.

2.4.1.5 Definitions of "heated solvent (hot solvent)" and "warmed solvent (warm solvent)"

The term "heated solvent" or "hot solvent" means a solvent heated almost to its boiling point.

The term "warmed solvent" or "warm solvent" generally means a solvent heated at 60 – 70°C.

2.4.1.6 Definitions of "cold extraction" and "warm extraction"

"Cold extraction" is performed at a temperature between 15°C and 25°C generally.

"Warm extraction" is performed at a temperature between 35°C and 45°C generally.

2.4.1.7 Definition of heating with a water bath, etc.

The term "heat on a water bath" indicates heating on a boiling water bath, unless otherwise specified; however, "a steam bath of about 100°C" can be used instead of "a water bath".

The term "heat with a reflux condenser" indicates boiling and refluxing the solvent, unless otherwise specified.

2.4.2 Notation of temperature

Express temperature in degrees Celsius attaching "°C" after Arabic numerals in accordance with the rule under **2.3** of this guideline.

2.4.3 Acceptable range in notation of temperature

When a temperature is given as a point value in a test procedure, the acceptable range of the temperature is generally ± 3°C.

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Do not use "about X °C" for the notation of the temperature, in principle. Instead, describe the temperature range in such manner as "37 ± 1°C" or "32 – 37°C" according to requirement in a test procedure.

2.4.4 Notation of column temperature in chromatography

Describe a column temperature in chromatography as "A constant temperature of about *XX*°C." and do not use the term "room temperature".

2.5 Pressure

2.5.1 Notation of pressure

Pascal is used as the basic unit as the notation of pressure in accordance with the rules under **2.3** of this guideline, and is used in the combination with supplemental units as needed.

2.5.2 Acceptable range in notation of pressure

When a pressure is given as a point value in a test procedure, the acceptable range is generally ± 10%. Do not use "about X kPa" for the expression of pressure in principle. Instead, describe a pressure range in such manner as "50 ± 2 kPa" according to requirement in a test procedure.

2.5.3 Definition of "reduced pressure"

The term "reduced pressure" indicates a pressure at 2.0 kPa or below, unless otherwise specified.

2.6 Time

2.6.1 Notation of time

Use "second", "minute", "hour", "day" and "month" for the expression of time.

Avoid using these units in combination, use a single unit which causes a smaller integer, and express in the same unit in the sentences related with each other, in principle.

[Example] Express "one hour 30 minutes" as "90 minutes" generally, not as "1.5 hours" or "5400 seconds".

2.6.2 Acceptable range in notation of time

When a time is given as a point value in a test procedure, its acceptable range is assigned as ±10% generally. However, this rule is not applied to those for the retention time of liquid chromatography and gas chromatography.

2.6.3 Definition of the term "immediately"

In the test procedure of drug, the description "immediately" generally means to start the next procedure within 30 seconds after the end of the previous procedure.

2.7 Mass percentage and concentration

2.7.1 Notation by percentage, and so on

For notation by percent, express mass percent and volume percent by the symbol of "%" and "vol%" respectively in accordance with the rules under **2.3** of this guideline.

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According to the General Notices of the JP, "w/v%" can be used only for expressing concentration such as formulation or ingredient concentration of preparations. However, when drafting a new JP monograph unless otherwise causing significant confusion, it is desirable to use the unit other than [w/v%] (such as [%] or [vol%]) except for Injections and Ophthalmic Liquid and Solutions, Peritoneal Dialysis Agents, and Ear Preparations for which the General Rules for Preparations specifies "the concentrations of the active ingredients expressed in percentage (%) means w/v%".

Use the symbols of "ppm" for mass parts per million, "ppb" for mass parts per billion, and "vol ppm" for volume parts per million, respectively. However, ppm used in Nuclear Magnetic Resonance Spectroscopy *<2.21>* in the General Tests indicates a chemical shift.

2.7.2 Notation using "in"

"A solution of AAA in BBB (*X* in *Y*)" means BBB solution of AAA which is prepared to be the same proportion as a solution in which *X* g (for solid reagent) or *X* mL (for liquid reagent) is dissolved in a solvent BBB to make *Y* mL.

"A solution of AAA (*X* in *Y*)" [or "AAA solution (*X* in *Y*)"] means an aqueous solution of AAA, which is prepared to be the same proportion to *X* g of AAA dissolved in water to make *Y* mL.

The value of *X* or *Y* shows a proportion but not an absolute weight or volume. In such a description, figures of *X* and *Y* should be the smallest integers. That is, (25 in 100) or (0.25 in 1) should be expressed as (1 in 4), for example.

[Example] "A solution of methyl parahydroxybenzoate in acetonitrile (3 in 4000)" is acetonitrile solution of methyl parahydroxybenzoate which is prepared to be the same proportion as a solution in which 3 g of methyl parahydroxybenzoate is dissolved in acetonitrile to make 4000 mL.

"A solution of sodium hydroxide (1 in 25)" means an aqueous solution of sodium hydroxide at the same proportion as a solution in which 1 g of sodium hydroxide is dissolved in water to make 25 mL.

(*Note: In the Japanese version, use "→" instead of "in".*)

2.7.3 Notation by molar concentration

For the expression of the concentration of a solution, molar concentration, etc. can be used in addition to the expressions described under **2.7.2.**

[Example] *X* mol/L AAA solution

2.7.4 Description of liquid mixture

Express the composition of a liquid mixture with inserting a slash "/" among each name of reagent/test solution. (*Note: This rule is applied to the Japanese version. In the English version, express as below.*)

The description "a mixture of AAA and BBB (10:1)" or "CCC, DDD and EEE (5:3:1)" denotes a mixture of 10 volumes of liquid AAA and 1 volume of liquid BBB, or a mixture of 5 volumes of CCC, 3 volumes of DDD and 1 volume of EEE. In this context, solvents should be mentioned in descending order of volumes and if their volumes are equal, follow the order in the case of same solubility described under **3.14.7.1**. Sequence of description of solvents.

[Example] "A mixture of acetone and hexane (3:1)" [do not express "A mixture of hexane and acetone (1:3)"].

2.7.5 Acceptable range in notation of concentration

The acceptable range of the concentration of solutions is generally ±10%.

2.8 Length

2.8.1 Notation of length

In accordance with the rules under **2.3** of this guideline, length is expressed in an integer with a single unit generally.

[Example] 2 m 10 cm should be expressed as 210 cm, and 2.5 cm should be expressed as 25 mm.

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2.8.2 Acceptable range in notation of length

When a length is given as a point value in a test procedure, its acceptable range is generally ±10%.

2.8.3 Size of apparatus, etc. in figure

Describe the size of apparatus in figures in the General Tests and Monographs in mm. The approximate figures are indicated by adding the word "about".

2.9 Mass

2.9.1 Notation of mass

In accordance with the rules under **2.3** of this guideline, describe "weigh *X* mg", "weigh accurately about *X* mg", or "weigh exactly *X* mg" for the notation of mass.

The term "weigh accurately about *X* mg" means to weigh down a sample within ±10% of the amount indicated to the degree of 0.1 mg using a chemical balance, or of 10 μg using a semi-micro balance. Select a chemical balance or a semi-micro balance by taking the digit number of the specification value into consideration.

When using a micro balance or an ultramicro balance, indicate its use and weigh down to the degree of 1 μg and 0.1 μg, respectively.

2.9.2 Definition of the term "weigh exactly"

The term "weigh exactly" means to weigh to the given decimal places.

The term "weigh exactly *X* mg" and "take *X* mg" have the same meaning, and they mean that the *X* mg is obtained by rounding off the actual value at the next digit of the given value.

"Weigh exactly 50 mg" means to weigh 49.5 – 50.4 mg

"Weigh exactly 50.0 mg" means to weigh 49.95 – 50.04 mg

"Weigh exactly 0.10 g" means to weigh 0.095 – 0.104 g

"Weigh exactly 2.000 g" means to weigh 1.9995 – 2.0004 g

"Weigh exactly 5 g" means to weigh 4.5 – 5.4 g

Specify the necessary digit number of the mass of a sample or a reagent considering that required for an actual measurement value.

2.9.3 Notation of mass unit

In principle, express the unit of mass as follows.

Less than 100 ng	ng
Not less than 100 ng and less than 100 μg	μg
Not less than 100 μg and less than 100 mg	mg
Not less than 100 mg	g

2.10 Volume

2.10.1 Notation of volume

In accordance with the rules under **2.3** of this guideline, describe "take *X* mL", "pipet *X* mL", or "make exactly *X* mL" for the notation of volume.

Especially when exact measurement is required for the volume of a sample or a reagent, use the word "exactly" or clearly indicate the use of a chemical volumeter such as a volumetric flask.

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[Example] "Pipet 5 mL of AAA, ..." generally means to use a 5-mL whole pipette. "Pipet X mL and add water to make exactly 100 mL" means to take exactly X mL in a 100-mL volumetric flask and add water to the marked line. "Add water to make 50 mL" generally means to use a graduated cylinder.

2.10.2 Notation of volume unit

In principle, express the unit of volume as follows.

Less than 100 µL	µL
Not less than 100 µL and less than 1 mL	mL (µL may be used as needed)
Not less than 1 mL and less than 5000 mL	mL
Not less than 5000 mL	L

2.11 Description for calculating formula

Describe in the order of the variable and the constant in the right-hand side of calculating formula. Describe the variable in algebraic expression. Do not describe the factor of the Standard Solution for Volumetric Analysis in the calculating formula.

2.11.1 Concerning expression of fraction

1) Use a slash mark to write a fraction in principle.

2) Do not parenthesize the fractional term written with a slash mark. Insert space before and after the slash mark.

Example of description: Amount (mg) of XX $= M_S \times A_T / A_S$

3) Do not express with a slash mark when it could cause misunderstanding or confusion, likely as the following examples.

① Fractional expression is included in the numerator or the denominator of fractional expression.

② The calculating formula includes triple or higher multiple parentheses and line feed is necessary in the right-hand side of calculating formula.

2.11.2 Number of digits for conversion factor including decimal fraction such as the conversion factor of molecular mass, etc.

Describe the conversion factor of molecular mass, etc. to three significant figures or to three decimal places in the calculating formula for spectrophotometry, chromatography, etc.

2.11.3 Description of constant

The description of constant terms is in the order of correction factor for dilution and conversion factor of molecular mass.

In Assay, Content uniformity, Dissolution, etc., describe the result of summation as one constant without separating the terms with respect to the correction factors for dilution, etc. other than the conversion factor of molecular mass.

In Purity, describe the result of summation of all constants as one constant except for the case where the conversion factor of molecular mass, etc. needs to be separated.

2.11.4 Explanation of constant

In the draft, the explanation of constant may be described to help understanding of calculating formula.

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2.12 Description method of the number of the General Tests

2.12.1 Policy of description of the number of the General Tests

Describe the number of the General Test with “< >” if it is referred to in the execution, judgment, etc. of the test which is taken as indicating standards for conformity to the General Rules for Preparations, the General Tests and the Official Monographs.

Do not describe the number of the general tests in the terms of Description of the Official Monographs not taken as indicating standards for conformity and the General Information, if not particularly necessary. In addition, do not describe the number in the case which is not accompanied by the implementation of testing, such as “Insoluble Particulate Matter Test for Injections is not applied to” and to the case of “Being specified separately ⋯” as well.

2.12.2 Concrete methods for description of the General Test number

2.12.2.1 Case where the name of the general test or the name to which the general test is applied

1) Case where the name of the test method is described as the same as that in the General Tests: Describe the General Test number immediately after the name of the general test.

[Example] as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, ⋯
as directed under Optical Rotation Determination <*2.49*>

2) Case where the name of the test item is not the same as the expression in the General Tests but the general test is applied to the test item: Describe the General Test number immediately after the name of test item.

[Example] Acid value <*1.13*> Not more than 0.2.
However, do not add the general test number to the words indicating the application of the relevant general test in the test item which has the general test number in the test item name.

[Example] Optical rotation <*2.49*> Ergotamine base $[\alpha]_D^{20}$: −155 - −165°. Dissolve 0.35 g of Ergotamine Tartrate ⋯. ⋯, and determine the optical rotation in a 100-mm cell.

3) Case where the words, not the same as the names of the General Tests but indicating the application of the relevant general test, are included in the text of the test item which does not have the general test number in the test item name: Describe the relevant number immediately after the “nominal phrase” meaning the application of the general test.

[Example] ⋯⋯, the melting point <*2.60*> is ⋯
⋯ determine the water <*2.48*> ⋯
⋯ determine the loss on drying <*2.41*> by ⋯.

For pH, do not add the general test number to the text indicating the operating procedure other than pass/fail judgment.

[Example] the solution adjusted to pH 3.0 with phosphoric acid

4) Case where the name of the general test or the “nominal phrase” meaning the application of the general test appears in multiple times in the text of the test item which does not have the general test number in the test item name: Describe the general test number as appropriate. Do not describe the general test number in duplicate unless otherwise causing misunderstanding or confusion.

[Example] Determine $[\alpha]_D^{20}$ in a 100-mm cell at 20±1°C as directed under Optical Rotation Determination <*2.49*>.

2.12.2.2 Case where the “nominal phrase” indicating specific stipulation of the relevant test method is put down with the general test name

1) Case where the general test name and the “nominal phrase” are described serially without intermediary of a postpositional article, etc.: Describe the general test number immediately after the “nominal phrase” described serially.

[Example] Atomic Absorption Spectrophotometry (Cold vapor type) <*2.23*>

2) Case where the general test name and the “nominal phrase” are described via “の” *(“under”)*, etc.: Describe the general test number immediately after the general test name.

[Example] as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>
the coulometric titration under Water Determination <*2.48*>
it responds to Qualitative Tests <*1.09*> (1) and (3) for ⋯. However, when only one of them is to be specified, describe as “it responds to Qualitative Tests (1) <*1.09*> for ⋯” (*Note: This precaution is applied to the Japanese version only.*)

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according to the cylinder-plate method as directed under Microbial Assay for Antibiotics <*4.02*>

2.12.2.3 Examples for special cases

Describe as “titrate <*2.50*>”.

[Example] titrate <*2.50*> with ⋯ (potentiometric titration).
titrate <*2.50*> with ⋯ (indicator: XX).
titrate <*2.50*> with ⋯: ⋯

2.13 Description method for international harmonization

2.13.1 Describing policy concerning international harmonization

Based on the General Notices 49, the harmonized General Test and the Monograph among the Japanese Pharmacopoeia, the European Pharmacopoeia and the United States Pharmacopeia (hereinafter referred to as the “Tripartite Pharmacopoeias”), are preceded by the statement as such. The parts of the text, being not harmonized, are surrounded by the symbols “◆ ◆” or “◇ ◇”. In addition, describe that information on the harmonization is available on the website of the Pharmaceuticals and Medical Devices Agency, and publish the URL of the website in the General Information on international harmonization.

2.13.2 Description method

2.13.2.1 Case of the General Tests

1) Case where the General Tests that have been harmonized completely by the Tripartite Pharmacopoeias are preceded by the statement as such.

[Example] This test is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia.
Information on the harmonization with the European Pharmacopoeia and the U.S. Pharmacopeia is available on the website of the Pharmaceuticals and Medical Devices Agency.

2) Case where the General Tests that have been harmonized by the Tripartite Pharmacopoeias, but the agreement of harmonization is incomplete are preceded by the statement as such..

[Example] This test 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 (◇ ◇).
Information on the harmonization with the European Pharmacopoeia and the U.S. Pharmacopeia is available on the website of the Pharmaceuticals and Medical Devices Agency.

2.13.2.2 Case of the monograph

1) Case where the monographs that have been harmonized completely by the Tripartite Pharmacopoeias are preceded by the statement as such..

[Example] This monograph is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia.
Information on the harmonization with the European Pharmacopoeia and the U.S. Pharmacopeia is available on the website of the Pharmaceuticals and Medical Devices Agency.

2) Case where the monographs that have been harmonized by the Tripartite Pharmacopoeias, but the agreement of harmonization is incomplete are preceded by the statement as such.

[Example] This monograph is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia. The corresponding part of 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 (◇ ◇).
Information on the harmonization with the European Pharmacopoeia and the U.S. Pharmacopeia is available on the website of the Pharmaceuticals and Medical Devices Agency.

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2.14 Others

2.14.1 Term of "meets the requirement"

State "AAA meets ..." for the description meaning "AAA has to meet ...".

2.14.2 Term of "dissolve"

State "dissolve 1.0 g of AAA in 20 mL of water" for the description meaning "add 20 mL of water to 1.0 g of AAA to dissolve". In addition, at the time of dissolving in the preparation of the standard solution and the sample solution, etc., do not describe the operations, such as "shake", for which there is no need to describe.

2.14.3 Meaning of "dry"

If "dry" is simply indicated for a sample, it means to dry the sample under the same conditions as described in the Loss on drying in the monograph.

2.14.4 Description about filtration

Specify the filtration apparatus when filtration is performed using some filter material other than filter paper. State the pore size of the filter when a glass filter or membrane filter is used. Describe the material of the filter, such as membrane filter, as needed.

When a glass filter is used, the filtration is performed by suction filtration unless otherwise specified.

2.14.5 Water used for tests

Unless otherwise specified, the water to be used in the tests of drugs shall be the water suitable for performing the relevant test, such as the water not containing any substance that would interfere with the test, and is described as "water".

2.14.6 Notation of aqueous solution

The solution that has only the name of solute in front of "solution" and the name of solvent is not given is an aqueous solution.

2.14.7 Amount of the test sample

Minimize the amount of the test sample without impacting on the test operation or precision control.

2.14.8 Description of operation for which the attention should be paid when performing the test

Describe the concrete operating conditions at the beginning of test procedure.

If the restriction of light exposure is required during the test, describe at the beginning of test procedure like as the following examples, and do not state "Conduct this procedure without exposure to daylight ...", in principle.

Case where test is performed under ordinary light protection (In the case of dissolution tests, it is not necessary to protect apparatuses from light, and use light-resistant vessels in analysis procedures.)

[Example] Conduct this procedure using light-resistant vessels.

Case where test is performed under stricter light protection (In the case of dissolution tests, perform the test with ingenuities such as darkening a test room, covering devices with an appropriate curtain.).

[Example] Conduct this procedure without exposure to light, using light-resistant vessels

Furthermore, in cases where the standard solution and the sample solution are unstable, etc., do not state "conduct this procedure rapidly", and describe the concrete conditions such as testing time and temperature.

Case where test is performed with specified testing time.

[Example] Conduct this procedure within 2 hours after preparation of the sample solution. (Gliclazide, etc.)

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Case where test is performed with specified conditions, such as storage temperature of the sample solution, etc.

[Example] Keep the sample solution and the standard solution at 5°C or below, and use them within 2 hours. (Ceftibuten hydrate, etc.)

2.14.9 Term of "diluted ..."

For a mixture of a test solution or a liquid reagent with water, the description "diluted …" can be also used in addition to the description with the component proportions (**2.7.4**).

"Diluted AAA (1 in *V*)" means AAA diluted in the same proportion with which water is added to 1 mL of AAA to dilute to *V* mL.

[Example] diluted hydrochloric acid (1 in 5)

diluted methanol (1 in 2)

diluted 0.01mol/L iodine VS (9 in 40)

diluted Matching Fluid for Color A (1 in 5)

2.14.10 Description of saturated solution

Express the saturated solution in which water is the solvent as "a saturated solution of [name of solute]" and in the case of the saturated solution of solvent other than water as "a saturated solution of [name of solute] in [name of solvent]".

[Example] A saturated solution of sodium chloride (aqueous solution saturated with sodium chloride)

A saturated solution of potassium hydroxide in ethanol (95) [ethanol (95) solution saturated with potassium hydroxide]

2.14.11 Utilization of reagent and test solution specified in JP

When establishing reagent and test solution, do not newly establish them without careful consideration, and investigate whether the existing ones can be applicable as much as possible. If the adoption of existing reagent and/or test solution is difficult, establish new one.

3. Official monographs

3.1 Contents and the order of the description in monographs

Describe the monograph with the items in the following order. Do not list unnecessary items from the viewpoint of assuring appropriately the description and quality of drugs. When there are more than one active pharmaceutical ingredients in a preparation, describe 10) Specifications of the content of the ingredient(s), 15) Identification, 21) Tests for preparations and 23) Assay, etc. for each ingredient in principle.

Although the following is focusing on the chemical drug substance, the items specific to the biologicals, crude drugs, etc. are annotated for such occasions.

(*Note: The order of items is applied in the Japanese version. In the English version, 1) Title in Japanese is placed after 3) Latin name. 4) Japanese synonym is not described and its English translation may be placed after 2) Title in English.*)

Items	Drug substance	Preparations
1) Title in Japanese	++	++
2) Title in English	++	++
3) Latin name (Describe for crude drugs)	+	+
4) Japanese synonym	+	+
5) Structural formula	++	--
6) Molecular formula and molecular mass (compositional formula and formula mass)	++	--
7) Chemical name	++	--

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8) Chemical Abstracts Service (CAS) registry number	++	--
9) Origin	+	+
10) Specifications of the content of the ingredient(s)	++	++
11) Labeling requirements	+	+
12) Method of preparation	--	++
13) Manufacture	+	+
14) Description	++	+
15) Identification	++	++
16) Specific physical and/or chemical values	+	+
17) Purity	++	+
18) Intentional adulteration	+	+
19) Loss on drying, Water or Loss on ignition	++	+
20) Residue on ignition, Total ash or Acid-insoluble ash	+	--
21) Tests for preparations	--	++
22) Other tests	+	+
23) Assay	++	++
24) Containers and storage	++	++
25) Shelf life	+	+
26) Others	+	+

Note: ++ : items to be listed in principle
+ : items to be listed as needed
-- : items unnecessary to be listed

3.1.1. Proper use of parenthesis, Arabic numerals and Roman numerals in test items

Use both parentheses when a monograph must meet all test items, and use a single parenthesis when it is sufficient to meet one of the test items. Roman numerals of item numbers are used when describing the order of the operation of a test in parts finely, when there are multiple tests in the same item, or when selecting a test, etc.

[Example] Purity
(1) Heavy metals
(2) Related substances

[Example] Description of crude drugs
1)
2)

[Example] Purity
(1) Perform the test according to the following i) or ii)
i)
ii)

3.2 Title in Japanese

3.2.1 Title in Japanese (hereinafter Japanese name) for a drug substance

Determine a Japanese name of a drug substance by referring to the Japanese Accepted Name for Pharmaceuticals (JAN) and the International Nonproprietary Names for Pharmaceutical Substances (INN). If JAN and INN are not available, refer to common names of the drug substance.

1) In the case where the pharmaceutically active moiety is an amine and the drug substance is its inorganic or organic salt, designate it as “XXXYYY 塩”.

[Example] アクラルビシン塩酸塩 (Aclarubicin Hydrochloride)
クロミフェンクエン酸塩 (Clomifene Citrate)

2) In the case where the pharmaceutically active moiety is a quaternary ammonium and the drug substance is its salt, designate it as “XXXYYY 化物”.

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[Example] アンベノニウム塩化物 (Ambenonium Chloride)
エコチオパートヨウ化物 (Ecothiopate Iodide)

3) In the case where the pharmaceutically active moiety is an alcohol and the drug substance is its ester derivative, designate it as "XXXYYY エステル".

[Example] ヒドロコルチゾン酪酸エステル (Hydrocortisone Butyrate)
エストラジオール安息香酸エステル (Estradiol Benzoate)

4) In the case where the pharmaceutically active moiety is a carboxylic acid and the drug substance is its ester derivative and at the same time in the case of using the abbreviation specified by INN as the name of the ester substituent, designate it by connecting the name of carboxylic acid and that of ester substituent with a full-width space.

[Example] セフロキシム　アキセチル (Cefuroxime Axetil)
セフテラム　ピボキシル (Cefteram Pivoxil)

5) For a hydrated drug substance, designate as "XXX hydrate". Do not specify the number of hydration water molecules even if it is not monohydrate (e.g. dihydrate or trihydrate etc.).

[Example] アンピシリン水和物 (Ampicillin Hydrate)
ピペミド酸水和物 (Pipemidic Acid Hydrate)

6) In the case where the drug substance is a clathrate compound of the pharmaceutically active moiety, designate it by combining the name of the pharmaceutically active moiety, that is the guest compound, and that of the host compound with a full-width space.

[Example] アルプロスタジル　アルファデクス (Alprostadil Alfadex)
リマプロスト　アルファデクス (Limaprost Alfadex)

7) In the case of L-amino acid and its derivative, attach "Lー" to the Japanese name.

[Example] Lーバリン (L-Valine), Lーカルボシステイン (L-Carbocisteine)

8) For a recombinant product, the name "XXX (Genetical Recombination)" is used.
9) For a product by cell culture, in principle, add the name of seed cell line in parenthesis to the name.
10) For an insulin derivative or an interferon, designate names by adding the word indicating the difference of the amino acid sequence subsequently with a full-width space after insulin and interferon.
11) For glycoprotein or glycopeptide whose amino acid sequence is common but sugar moiety varies, designate names by adding a full-width space and then *Katakana* expression of Greek alphabet [アルファ (for α), ベータ (for β) and ガンマ (for γ) etc.] after the name.
12) For a chemically modified peptide or protein, etc., where a two-word naming scheme is given in the INN, the name should be a two-word name in the same way as in the INN, with a full-width space between the two words.
13) With respect to a biological, in the case of an aqueous solution, describe that it is an aqueous solution in the origin section, and do not add the Japanese word corresponding to "solution" or "aqueous solution" in the Japanese name.
14) Express the Japanese name of crude drugs in *Katakana*.
When a space is used for the Japanese name of a drug substance, describe the name without a space in the section origin and below.

3.2.2 Japanese name for a preparation

Give a Japanese name to a preparation generally by combining the name of active ingredient with the name indicating the dosage form.

For the name indicating dosage form, when the preparation falls under the subclassification of General Rules for Preparations (Orally Disintegrating Tablets/Orodispersible Tablets, Dry Powder Inhalers, etc.) use the name of the dosage form. When the preparation does not fall under the subclassification but falls under middle classification (Tablets, Injections, etc.), use the name of the dosage form under the middle classification. Dosage forms other than those listed in the Monographs for Preparations and the Monographs for Preparations Related to Crude Drugs can also be used as necessary. For example, the name of preparation suitable for description or usage, etc. can be used by combining the route of administration and the name of the dosage form in the Monographs for Preparations, etc. The Japanese name of a drug substance is used for the name of a preparation containing it as a single active ingredient. For a preparation containing multiple active ingredients, their Japanese names are generally arranged in the order of the Japanese syllabary. One or more representatives can be arranged in the order of the Japanese

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syllabary, unless otherwise inconvenience. Important active ingredients can be placed first depending on the development process. However, if the drug substance is a hydrate, do not use “hydrate” in the Japanese name of a preparation. In addition, if a -trivial name, etc. is widely used as the name of a preparation in the medical front, and is not derived from a specific brand name, the name may be used unless it causes any confusion. Furthermore, express the concentration of a triturated powder by %, and do not use the term of “triturated powder”.

[Examples] アザチオプリン錠 (Azathioprine Tablets)
カイニン酸・サントニン散 (Kainic Acid and Santonin Powder)
イオウ・サリチル酸・チアントール軟膏 (Sulfur, Salicylic Acid and Thianthol Ointment)
コデインリン酸塩散 1% (1% Codeine Phosphate Powder)

3.3 Title in English (hereinafter English name)

Make English name of a drug substance correspond to its Japanese name.

Make English name of a preparation correspond to its Japanese name unless the naming causes any problem. In addition, refer to the dosage form name used in the United States Pharmacopeia, European Pharmacopoeia, etc.

Start each word of English name with capital letter.

The English name of Kampo formulae used for Kampo formulation extract follows the unified expression rule (Standard Kampo Formula Nomenclature) of the major related academic societies. References: *Kampo Medicine* **56** (4), 609-622 (2005); *Journal of Traditional Medicines* **22,** Bound-in supplementary volume (2005); *Natural Medicines* **59** (3), 129-141 (2005).

3.4 Japanese synonym

In principle, a Japanese synonym of a drug substance is not set. If a Japanese name of a drug substance is different from Japanese rendering of the INN, or from the name that has been widely used, these can be described as the Japanese synonym.

For a preparation, if necessary, a Japanese synonym may be used as the name of the part of an active ingredient of the preparation. Also, if a traditional name of the preparation is widely used in the medical field, and which is not derived from a specific brand name, the name may be used as a Japanese synonym.

When a Japanese name of a drug substance or preparation is revised, describe its former name as the Japanese synonym as necessary.

If the non-proprietary name written in approval certificate differs from the Japanese name, describe it as the Japanese synonym.

For crude drugs, a Japanese name expressed with *Kanji* characters should be listed as the Japanese synonym.

(*Note: In the English version, Japanese synonym is not described. Its Japanese name is described in Katakana*.)

3.5 Latin name

For crude drugs, the Latin name of the crude drug is an international name written next to the English name. The Latin name should be a combination of the generic name and the medicinal part of origin of the crude drug. If there are other crude drugs from the congeners, add the specific epithet or the Latin expressing the morphological characteristics, alias, etc. of the crude drug. However, use a conventional Latin name of the crude drug if available.

3.6 Structural formula

Prepare the structural formula according to the WHO guideline for description of chemical structural formula, “The graphic representation of chemical formulae in the publications of international nonproprietary names (INN) for pharmaceutical substances (WHO/Pharm/95.579), https://apps.who.int/iris/handle/10665/63585”. Furthermore, in case where the compound has a geometric isomer or a stereoisomer or is a racemic mixture, the structural formula of the compound concerned should be the one reflecting that it has an isomer, in principle. If the stereo configuration of the compound has been determined, the stereo notation of the structure of the part is shown using a wedge line and a dotted line. If the compound is known to be a mixture, the structure is indicated as an *R*-form using a wedge line and a dotted line, and the racemic form is indicated with adding "and enantiomer" without a "*". For diastereomers, the asymmetric carbon concerned is marked with a "*", and "and epimer at C*" is

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indicated at the bottom right of the structural formula. For geometric isomers, the carbon concerned is marked with a "*", and "and geometric isomer at C* " is indicated at the bottom right of the structural formula.

Express the amino acid sequence of a peptide drug or a protein drug by three letter codes (approximately 20 amino acid residues or less) or one letter codes (approximately 21 amino acid residues or more). In the one letter code expression, add a space at every 10 residues and start a new line at every 50 residues. Also, explicitly describe the structural information such as disulfide bonds and post-translational modifications, etc. Describe peptide drugs and protein drugs generally as below. In addition, describe the amino acid sequence by using monospaced fonts for the one letter code.

[Example 1] Peptide drug;

Glu-Ile-Val-Glu-Gln-Cys-Cys-Thr-Ser-Ile-Cys-Ser-Leu-Tyr-Gln-Lue-Gln-Asn

Glu1, Pyroglutamic acid

[Example 2] Peptide drug and Protein drug (two chains);

```
A chain   MIVEQCCTSI   CSLYQLENYA   CGEAGFFTPE   G

B chain   GIVEQCIYVL   LENYIALYQL   PVCQHLCGSH   LVAAK
```

A chain M1: formylated; A chain G31: amidated

B chain: K35, processing, partial

[Example 3] Protein drug (homodimer);

```
APAERCELAA ALAGLAFPAP RGYSLGNWVC AEPQPGGSQC VEHDCFALYP
AAKFESNFNT QATNRNTDGS TDYGILQINS GPATFLNASQ ICDGLRGHLM
RWWCNDGRTP GSRNLCNIPC SALLSSDITA TVRSSVAADA ISLLLNGDGG
SVNCAKKIVS DGNGMNAWVA WRNRCKGTDV QLPPGCGDPK RLGPLRGFQW
QAWIRGCRLV FPATCRPLAV GAWDESVENG GCEHACNAIP GAPRCQCAGP
AALQADGRSC TASATQSCND LCEHFCVPNP DQPGSYSCMC ETGYRLAADQ
HRCEDVDDCI LEPSPCPQRC VNTQGGFECH CYPNYDLVDG ECVEPVDPCF
RANCEYQCQP LNQTSYLCVC AEGFAPIPHE PHRCQMFCNQ TACPADCDPN
TQASCSCPEG YILDDGFICT DIDECENGGF CSGVCTNLPG TFECIGPDK
```
2

C245-C245: Inter-subunit disulfide bond

[Example 4] Glycoprotein drug;

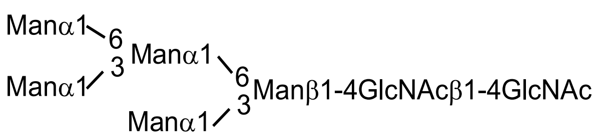
Protein moiety

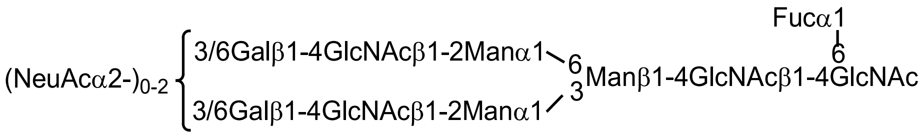
```
APAERCELAA ALAGLAFPAP RGYSLGNWVC AEPQPGGSQC VEHDCFALYP
AAKFESNFNT QATNRNTDGS TDYGILQINS GPATFLNASQ ICDGLRGHLM
RWWCNDGRTP GSRNLCNIPC SALLSSDITA TVRSSVAADA ISLLLNGDGG
SVNCAKKIVS DGNGMNAWVA WRNRCKGTDV QLPPGCGDPK RLGPLRGFQW
QAWIRGCRLV FPATCRPLAV GAWDESVENG GCEHACNAIP GAPRCQCAGP
AALQADGRSC TASATQSCND LCEHFCVPNP DQPGSYSCMC ETGYRLAADQ
HRCEDVDDCI LEPSPCPQRC VNTQGGFECH CYPNYDLVDG ECVEPVDPCF
RANCEYQCQP LNQTSYLCVC AEGFAPIPHE PHRCQMFCNQ TACPADCDPN
TQASCSCPEG YILDDGFICT DIDECENGGF CSGVCTNLPG TFECIGPDK
```

N87, N362, T436: glycosylation; N389: glycosylation, partial

Carbohydrate moiety (structures of major glycan)

N87, N362, N389





T436

NeuAcα2-6Galβ1-3GalNAc

3.7 Molecular formula and molecular mass (Compositional formula and formula mass)

3.7.1 Organic and inorganic substance

Describe a molecular formula and molecular mass for an organic compound, and a compositional formula and formula mass for an inorganic compound.

3.7.2 Notation of molecular formula

Align molecular formula with the expression of structural formula.

Regarding the order of elements, molecular formula of an organic compound should begin with C and then H, followed by other elements in the alphabetical order of symbols of the elements. For salt-forming compounds, solvates, clathrate compounds, insert "·" between each molecular formula [Example 1]. Express in principle the coefficients of molecular formula by integers [Example 2]. However, for solvates, fractional number (including mixed fraction) can be used as the coefficient of molecular formula of the solvent [Example 3]. If the number of salt or solvent is unknown, describe the coefficient by using *x*, *y*, etc. [Example 4].

[Example 1] $C_6H_{14}N_4O_2 \cdot HCl$
$C_{16}H_{10}ClKN_2O_3 \cdot KOH$
$(C_{18}H_{22}N_2S)_2 \cdot C_4H_6O_6$
$C_{37}H_{67}NO_{13} \cdot C_{12}H_{22}O_{12}$
$C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$
$C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$
$C_{18}H_{18}N_6O_5S_2 \cdot C_3H_8O_2$
$C_4H_{10}N_2 \cdot C_6H_{10}O_4$
$C_{12}H_{15}NO_3 \cdot HCl \cdot H_2O$
$C_{15}H_{15}N_3O \cdot C_3H_6O_3 \cdot H_2O$

[Example 2] $C_{16}H_{19}N_3O_5S \cdot 2H_2O$
$C_{16}H_{20}N_7NaO_7S_3 \cdot 7H_2O$
$(C_{12}H_{19}NO_2)_2 \cdot H_2SO_4$
$(C_{18}H_{22}N_2S)_2 \cdot C_4H_6O_6$
$C_{20}H_{24}ClN_3S \cdot 2C_4H_4O_4$
$(C_{20}H_{41}N_5O_7)_2 \cdot 5H_2SO_4$
$C_{19}H_{24}N_6O_5S_2 \cdot 2HCl \cdot H_2O$
$(C_{16}H_{18}N_2O_4S)_2 \cdot C_{16}H_{20}N_2 \cdot 4H_2O$
$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$

[Example 3] $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$
$C_{22}H_{24}N_2O_8 \cdot HCl \cdot \frac{1}{2}C_2H_6O \cdot \frac{1}{2}H_2O$
$C_{42}H_{66}O_{14} \cdot \frac{1}{2}C_3H_6O$

[Example 4] $C_{22}H_{43}N_5O_{12} \cdot xH_2SO_4$
$C_{20}H_{18}ClNO_4 \cdot xH_2O$
$C_{14}H_{16}N_8O_4 \cdot C_2H_8N_2 \cdot xH_2O$

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$C_{22}H_{36}O_5 \cdot xC_{36}H_{60}O_{30}$
$C_{12}H_{30}Al_8O_{51}S_8 \cdot xAl(OH)_3 \cdot yH_2O$

3.7.3 Representation of molecular mass (formula mass)

To calculate molecular mass (formula mass), sum up the atomic weight of each element as it is, based upon the Table of International Atomic Weight 2015-Table of Atomic Weight (2017) (The Chemical Society of Japan Atomic Weight Committee). However, the atomic weight of elements shown in the range of variation in the 2015 Table of International Atomic Weight should be based on the Table of International Atomic Weight 2007-Table of Atomic Weight (2010) (The Chemical Society of Japan Atomic Weight Committee). The summed value is rounded off from three decimal places and determined to two decimal places.

3.7.4 Pause between molecular formula and molecular mass

Insert ":" between molecular formula (compositional formula) and molecular mass (formula mass).

[Example] $C_9H_8O_4$: 180.16

3.7.5 Description of molecular formula and molecular mass of biologicals

For peptide drug or protein drug having homogeneous molecular formula and molecular mass, describe their molecular formula and molecular mass. For glycoprotein drug or modified protein drug having heterogeneous molecular formula and molecular mass, describe only the molecular formula and molecular mass of the protein moiety, and describe the molecular mass (approximate figure) including the sugar chains and modification groups in the origin. For the peptide drug, protein drug and glycoprotein drug, describe generally as follows.

[Example 1] Peptide drug (3.6, Example 1);

$C_{86}H_{137}N_{21}O_{31}S_3$: 2057.33 (Note)

Note Calculate the N-terminal, C-terminal and side chain in non-dissociative form. In addition, calculate Glu1 as pyroglutamic acid.

[Example 2] Peptide drug or protein drug (3.6, Example 2);

$C_{326}H_{499}N_{79}O_{97}S_8$: 7333.44 (two chains) (Note 1)
A-chain $C_{148}H_{221}N_{35}O_{49}S_5$: 3434.87 (Note 2)
B-chain $C_{178}H_{280}N_{44}O_{48}S_3$: 3900.59

Note 1 Calculate the N-terminus, C-terminus and side chain in non-dissociative form. Calculate the intrachain and interchain disulfide bonds in bound form. Calculate M1 in A-chain as formyl methionine. Calculate G31 in A-chain as glycinamide. In addition, calculate K35 in B-chain assuming that it is bound.
Note 2 Calculate the intrachain disulfide bond in bound form. Calculate the Cys residue, contributed to the interchain disulfide bond, as a reduced form.

[Example 3] Protein drug (3.6, Example 3);

$C_{4078}H_{6216}N_{1186}O_{1314}S_{100}$: 96086.65 (dimer) (Note 1)
Monomer $C_{2039}H_{3109}N_{593}O_{657}S_{50}$: 48044.33 (Note 2)

Note 1 Calculate the N-terminal, C-terminal and side chain in non-dissociative form. Calculate the intrachain and interchain disulfide bonds in bound form.
Note 2 Calculate the intrasubunit disulfide bond in bound form. Calculate the Cys residue, contributed to the intersubunit disulfide bond, as a reduced form.

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[Example 4] Glycoprotein drug (3.6, Example 4);

$C_{2039}H_{3109}N_{593}O_{657}S_{50}$: 48044.33 (protein moiety) (Note)

Note Calculate the N-terminal, C-terminal and side chain in non-dissociative form. Calculate the intrachain disulfide bonds in bound form. Calculate N87, N362, N389, T436 and S285 assuming they are free from sugar.

3.8 Chemical name and Chemical Abstracts Service (CAS) registry number

3.8.1 Naming of a chemical name

Denominate a chemical name in English according to IUPAC nomenclature, and begin with a capital letter. Furthermore, in case where the compound has a geometrical isomer or a stereoisomer or is a racemic mixture, the chemical name of the compound concerned should be the one reflecting that it has an isomer, in principle.

3.8.2 Description of CAS registry number

Indicate the CAS registry number in italics with [ ] under the chemical name. If the chemical name is not described, indicate the number under the molecular formula (compositional formula). If CAS registry number corresponding to the substance of the monograph is not available, indicate the number of its anhydrate, etc. in such manner as [*AA-BB-C*, anhydrate].

3.9 Origin

3.9.1 Description for origin

For a drug substance, generally describe the origin except for that chemically synthesized.

For a preparation manufactured with a drug substance other than that chemically synthesized as an active ingredient or manufactured from natural substances, generally describe the origin when the drug substance is not listed in the JP.

For a polymeric compound, explicitly describe the origin such as the synthetic raw materials.

For an antibiotic manufactured by culture, describe the scientific name (Latin) of the producing strain.

[Example] Antibiotic (Gentamicin Sulfate)

"Gentamicin Sulfate is the sulfate of a mixture of aminoglycoside substances having antibacterial activity produced by the growth of *Micromonospora purpurea* or *Micromonospora echinospora*."

With respect to a biological, explicitly describe it as an aqueous solution when it is in an aqueous solution form. Describe the molecular mass in the origin according to 3.7.5, as necessary. When the monograph has the test item for molecular mass, describe its specification value. Molecular mass can be expressed in a range (example: *XX* – *YY*). In the case where the molecular mass is not included as the test item and cannot be calculated due to the high heterogeneity, etc., the value obtained by summing up the atomic weight of each element for the representative molecule can be described. For recombinant glycoprotein drugs, explicitly describe clearly the kind of host cell substrate. Describe the biologicals including recombinant drugs generally as follows.

Peptide drug (3.6, Example 1)

[Example] "XXX is a (hormone, enzyme, cytokine, growth factor, vaccine, antibody, blood coagulating factor, inhibiting factor or the like) obtained from YYY (cell, tissue or organ, etc.) of (healthy) ZZZ (species). It is a peptide consisting of 18 amino acid residues."

"XXX is a synthetic (hormone, enzyme, cytokine, growth factor, vaccine, antibody, blood coagulating factor, inhibiting factor or the like). It is a peptide consisting of 18 amino acid residues."

Peptide drug or protein drug (3.6, Example 2)

[Example] "XXX is an aqueous solution in which a desired product is a (hormone, enzyme, cytokine, growth factor, vaccine, antibody, blood coagulating factor, inhibiting factor or the like) obtained from YYY (cell, tissue or organ, etc.) of

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(healthy) ZZZ (species). It is a PPP (peptide or protein) consisting of one A chain consisting of 31 amino acid residues and one B chain consisting of 35 amino acid residues."

Protein drug (3.6, Example 3)

[Example] "XXX is a (hormone, enzyme, cytokine, growth factor, vaccine, antibody, blood coagulating factor, inhibiting factor or the like) obtained from YYY (cell, tissue or organ, etc.) of (healthy) ZZZ (species). It is a protein consisting of two subunits consisting of 449 amino acid residues.

Glycoprotein drugs (3.6, Example 4)

[Example] "XXX is an aqueous solution in which a desired product is a (hormone, enzyme, cytokine, growth factor, vaccine, antibody, blood coagulating factor, inhibiting factor or the like) obtained from YYY (cell, tissue or organ, etc.) of (healthy) ZZZ (species). It is a glycoprotein (molecular mass about *MM*, or *NN* to *MM*) consisting of 449 amino acid residues."

Recombinant peptide drugs and protein drugs

[Example] " XXX (Genetical Recombination) is an aqueous solution in which a desired product is a recombinant human DDD. It is a PPP (peptide or protein) consisting of *NN* amino acid residues."

Recombinant glycoprotein drugs

[Example] " XXX (Genetical Recombination) is an aqueous solution in which a desired product is a recombinant human DDD and produced by the CCC cell. It is a glycoprotein (molecular mass about *MM*) consisting of *NN* amino acid residues."

Recombinant glycoprotein drugs (amino acid substituent)

[Example] " XXX (Genetical Recombination) is an aqueous solution in which a desired product is a derivative of recombinant human YYY, and its #th and &th amino acid residues of $ chain were substituted to Eee and Fff (three letter code for amino acid), respectively. It is a glycoprotein (molecular mass about *MM*) consisting of *NN* amino acid residues produced by the CCC cell."

Polysaccharide

[Example] "XXX is a YYY (example: glycosaminoglycan, low-molecular-mass heparin) (molecular mass about *MM*) consisting of AAA obtained (by DD decomposition of PPP [example: heparin sodium)] from QQQ (cell, tissue or organ, etc.) of (healthy) RRR (species) and BBB (monosaccharide).

3.9.2 Description of scientific name

Describe the scientific name of the plant for a crude drug according to "The International Plant Names Index (IPNI), http://www.ipni.org/". However, describe the surname of the author of the scientific name in full spelling, and omit the author name of the basionym.

[Example] Although the scientific name of "Mitsubaakebi" is described as *Akebia trifoliata* (Thunb.) Koidz. by IPNI, describe it in JP as *Akebia trifoliata* Koidzumi.

For the family name, follow the Modified Engler System.

In addition, when the crude drug has multiple origins, and different requirements in items according to each origin, describe the origins with numbers such as 1), 2), · ·.

3.9.3 Starting of the description of the origin

Begin the description of the origin with "XXX is ⋯"

If it is necessary to describe the characteristics of a preparation, describe as follows.

[Example] XXX is an aqueous injection.

[Example] XXX is a preparation for syrup, which is dissolved (suspended) before use.

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3.10 Specifications of the content of ingredient(s)

3.10.1 Description for a drug substance

The content of the ingredient of a drug substance is described generally as follows. (*Note: Examples shown below are for the English version.*)

Chemical drug

[Example] "XXX *(title of monograph)* contains not less than *XX* % and not more than *YY* % of AAA (molecular formula)."

Antibiotic in which the origin is described.

[Example] "It contains not less than *XX* μg (potency) and not more than *YY* μg (potency) per mg, calculated on the anhydrous basis. The potency of XXX *(title of monograph)* is expressed as mass (potency) of ZZZ (molecular formula: molecular mass)."

Protein drugs (solution)

[Example] "It contains not less than *XX* mg and not more than *YY* mg of protein per mL, and not less than *ZZ* units and not more than *WW* units per mg of protein."

Protein drugs (powder)

[Example] "It contains not less than YYY *ZZ* units and not more than YYY *WW* units per mg of protein."

Crude drug

Describe "XXX *(title of monograph)* contains…" like in the Official Monograph other than Crude drugs. . (*Note: In the English version, begin with "It" if the origin is described.*)

[Example] "It contains not less than *X.X* % of ZZZ (molecular formula)."

"It contains not less than *X.X* % of ZZZ (molecular formula), calculated on the basis of dried material."

When the assay is performed using Reference Standard.

[Example] "It contains not less than *XX* % of ZZZ (molecular formula: molecular mass), calculated on the basis of dried material."

When the assay is performed using ZZZ for assay.

[Example] "It contains not less than *XX* % of ZZZ, calculated on the basis of dried material."

Do not use "Component determination" as the test item name in monograph and describe it as "Assay".

3.10.2 Description for a preparation

The content of the active ingredient of a preparation is described generally as follows.

Preparation (in general)

[Example] "XXX *(title of monograph)* contains not less than *XX* % and not more than *YY* % of the labeled amount of ZZZ (molecular formula: molecular mass)."

Injections (formulation is not stipulated) and XXX for Injection

[Example] "It contains not less than *XX* % and not more than *YY* % of the labeled amount of ZZZ (molecular formula: molecular mass)."

Injections (formulation is stipulated)

[Example] "It contains not less than *XX* w/v% and not more than *YY* w/v% of ZZZ (molecular formula: molecular mass)."

Furthermore, in any test of identification, purity, content uniformity, dissolution and assay, the description of "according to the labeled amount" is not required.

3.10.3 Name of a drug in monograph and name of a chemically pure substance in the specification value for content of ingredient

In the acceptance criterion for the content of the ingredient, describe the specific name of a drug in the Official Monographs or the name of a chemically pure substance generally according to the following rules.

Indicate the name of a drug in the Official Monograph in parentheses「 」.

(Note: Parenthesis is not used, and the first letter of the name is capitalized in the English version).

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Indicate the name of a chemically pure substance with the molecular formula or the compositional formula in parentheses ( ) after the drug name or ingredient name. If the molecular mass or formula mass corresponding to the name is not shown in the Official Monograph, describe the molecular mass or formula mass following the molecular formula or the compositional formula.

[Example]

(1) In the case of showing the name of a drug specified in the Official Monograph

(Japanese name in the Monograph)	(Example)
アミノフィリン注射液 (Aminophylline Injection)	「アミノフィリン水和物」(Aminophylline Hydrate)

(2) In the case of showing the name of a chemically pure substance whose molecular mass or formula mass is given in the Official Monograph

(Japanese name in the Monograph)	(Example)
レセルピン (Reserpine)	レセルピン($C_{33}H_{40}N_2O_9$) [reserpine ($C_{33}H_{40}N_2O_9$)]
塩化ナトリウム (Sodium Chloride)	塩化ナトリウム(NaCl) [sodium chloride (NaCl)]

(3) In the case of showing the name of a chemically pure substance of which molecular mass or formula mass is not given in the Official Monograph

(Japanese name in the Monograph)	(Example)
レセルピン散 0.1% (0.1% Reserpine Powder)	レセルピン($C_{33}H_{40}N_2O_9$: 608.68) (reserpine [$C_{33}H_{40}N_2O_9$: 608.68)]
生理食塩液(Isotonic Sodium Chloride Solution)	塩化ナトリウム(NaCl: 58.44) [sodium chloride (NaCl: 58.44)]

3.10.4 Description of the specification value for content

3.10.4.1 In stipulating with "%"

Show the content of an ingredient with % generally down to one decimal place regardless of a drug substance or preparation.

Indicate the specification value for the content of a drug substance generally in a range.

Indicate the specification value for the content of an ingredient of a preparation by % to the labeled amount with a range.

When the assay for an ingredient of a drug substance is performed by liquid chromatography, describe the specification of the content of the ingredient of the drug substance as 98.0 – 102.0% generally.

3.10.4.2 In stipulating with unit or potency

Indicate with "unit" when the content of an ingredient is expressed as potency, a definite amount of biological effect. For an antibiotic, however, indicate the potency generally by "mass (potency)". The unit mentioned in the JP represents the JP Unit.

Indicate the specification value for the amount of the ingredient generally in a range.

3.10.5 Description on content of ingredients assayed after drying, etc.

Describe "XXX (*title of monograph*), when dried, contains ..." if a drug is assayed after drying under the conditions for Loss on drying. Describe "XXX (*title of monograph*) contains ..., calculated on the dried basis" if a drug is calculated on the actual measurement value from Loss on drying. Select either of both arbitrarily. Describe "XXX (*title of monograph*) contains ..., calculated on the anhydrous basis" if a drug is calculated on the actual measurement value from Water. In this case, calculate on the desolvent basis if the limit of residual solvent is controlled and the amount of the residual solvents may give any impact on the assay. Describe "XXX (*title of monograph*) contains ... calculated on the anhydrous and residual solvent-free basis." (Example: Pravastatin Sodium, etc.) In addition, when the residual solvent is concretely specified such as ethanol in the Purity, describe "XXX (*title of monograph*) contains ..., calculated on the anhydrous and ethanol-free basis." (Example: Sodium Aurothiomalate, etc.)

3.10.6 Others

For an organic halide whose assay method has been established appropriately, it is unnecessary to specify the halogen content in addition to that for the content of the ingredient. Specify the halogen content as the specific physical and/or chemical values, not as the content of the ingredient.

Furthermore, on specifying the content of the ingredient for a preparation, do not specify it based on the overage in principle.

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3.11 Labeling requirements

In the case when a labeling requirement is prescribed, describe as below. Labeling requirements other than the following examples may be described as necessary, taking account of the characteristics of a drug.

① When it is necessary to concern the item of labeling (value, property, unit, etc.)

[Example] X of XXX is expressed as mass (potency) of AAA.
X of XXX is expressed as the unit of AAA.

② When a drug is classified by type, application, etc.

[Example] The label states the type (of XX).
For XXX used for XX, the label states the purpose.

③ When there is a possibility that a certain substance is added for maintaining quality etc.

[Example] The label states the addition in the case where AAA is added as XX agent.
The label states the use or nonuse of XX agent and its components.

④ When an alternative name can be shown

[Example] When XX of XXX is not more than YY, it may be labeled ZZZ as the alternative name.

⑤ When processed or there are multiple processes

[Example] The label states the fact where it is XXX.
The label states the process.

3.12 Method of preparation

When the manufacturing method is described in the dosage form of General Rules for Preparations, describe generally as follows, using the name of the dosage form.

[Example] Prepare as directed under Tablets, with AAA.
[Example] Prepare as directed under Syrups, with AAA.
[Example] Prepare as directed under Granules or Powders, with AAA.

3.13 Manufacture

For a drug whose quality is extremely difficult to ensure only with the specifications of the final product, matters to be taken into consideration in manufacturing processes are established as Manufacture in addition to the specifications, as necessary. When establishing a specific test method and an acceptance criterion, describe them with reference to the description examples referring to the case where it is necessary to satisfy the test method and the acceptance criterion, the conditions etc. In addition, when describing a concrete test method in Manufacture, describe it according to the description procedure described in "3. Official monographs".

(Examples of Manufacture)

・Requirements concerning raw materials, materials and manufacturing processes: restriction of impurities having the risk of contamination or generation in raw materials, materials and manufacturing processes.
・Requirements concerning the control of intermediates: acceptance criteria in the case of assuring the quality of final products by control of intermediates such as a final intermediate.
・Requirements concerning in-process testing: In the case of assuring the quality of final products by in-process tests such as the control of a purification level etc.
・Requirements concerning the omission of tests for release: Conditions of parametric release, real time release testing, skip testing and so on when they are applied.

[Example] AAA is manufactured with XXX derived from XX as a source material, and evaluate the contamination of YYY, a DNA reactive (mutagenicity) impurity, in the manufacturing process.
[Example] Manufacture AAA by the method that eliminate or minimize XXX having pharmacological activity of XX. The manufacturing method must be verified to meet the following tests.
YY test To *X* g of AAA ⋯, perform the YY test: it meets the requirement.

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[Example] Since AAA is optically active, the manufacturing method must be verified that AAA meets the specification of optically active impurities in the final XXX by stipulating appropriately an optical purity in the control of intermediates and processes.

[Example] AAA is obtained by XX of XXX. The intermediate YYY meets the following tests.
YY test To *X* g of AAA ···, perform YY test: YYY is not more than *XX*%.

[Example] In the purification process of AAA, perform the purification so that XXX in the final product is not more than *XX*%.

The quality of a biological product is ensured by performing the control of manufacturing processes appropriately in addition to establishing the specifications and test methods of a drug substance or a drug product. Describe manufacture for the quality attributes which should be controlled but have no specification and test method. As a process to avoid the contamination of infectious substances is a premise for all biological products, it is not necessary to describe the manufacture regarding infectious substances in monographs.

1) In the case of establishing in-process testing

[Example] Host cell proteins
Example 1: Determine the residual amount of host cell proteins by an enzyme immunoassay as an in-process test: not more than the control value.
Example 2: Determine the residual amount of host cell proteins by an enzyme immunoassay as an in-process test: not more than *XX*.
Example 3: Use the eluate of XX chromatography as a sample solution. Determine the residual amount of host cell proteins by an enzyme immunoassay: not more than the control value.
Example 4: Use the eluate of XX chromatography as a sample solution. Determine the residual amount of host cell proteins by YY using ZZ: not more than *XX*.

[Example] Non-glycosylated proteins
Perform the XX test using YY method as an in-process test: non-glycosylated protein is not more than *XX*%.

[Example] Intermediates
Regard the product immediately before XX process as an important intermediate and prescribe test methods and pass/fail criteria concerning YY, ZZ and WW.

2) In the case of the quality attribute is controlled by process parameter without establishing in-process testing

[Example] Oligosaccharides
Production cells are cultured by the method which is verified to obtain the similar oligosaccharide profile as the reference standard when N-linked oligosaccharides of a drug substance is tested by a method based on Glycosylation Analysis of Glycoprotein <*2.64*>.

[Example] Host cell DNA
Purification is performed by the method which is verified to be able to reduce the residual amount of DNA in a drug substance to not more than the control value when determined by a PCR method.

[Example] Related substances
Purification is performed by the method which is verified to be able to reduce the area of the peaks other than the principal peak to less than *XX* % and the total area of the peaks other than the principal peak to less than *YY*% when determined by ion exchange chromatography using the drug substance as a sample.

[Example] Non-glycosylated proteins
Purification is performed by the method which is verified to be able to reduce the non-glycosylated proteins in a drug substance to not more than *XX* %.

3.14 Description

Description states physical and chemical properties and form of a drug for reference.

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3.14.1 Description

3.14.1.1 Items of Description

State the Description of a drug substance, as needed, in the order of color, form, odor, taste, solubility, acidity or alkalinity of solution, physical and chemical characteristics (hygroscopicity, changes due to light, etc.), and specific physical and/or chemical values (not regarded as the pass/fail criteria). When a melting point is a decomposition point and its specification is necessary, describe it in the item of the Description in principle. Regarding the melting point of a drug substance to be proved to be polymorphic, describe the melting point of the drug substance, whose spectrum is used as the reference spectrum, in the item of the Description as the information of physical property, not in the item of specific physical and/or chemical values indicating pass/fail criteria, regardless of whether the presence or absence of the patent.

Since the characteristics of preparations are different for each product, do not state the Description generally. However, for example, state the physical appearance of injections and ophthalmic solutions, and the physical appearance, odor and taste (only for preparations for oral use) in this order for preparations formulated in pharmacy. If the preparation shows the different stability and the characteristic value from those of the drug substance by formulation, mention these in this order.

In describing the specific physical and/or chemical values, follow the manner shown under 3.17.

For the preparation of which drug substance is not listed in JP for some reason, state in principle the Description (the solubility, the acidity or alkalinity of solution, etc.) of the drug substance to be used according to the manner of the Description of a drug substance.

(Example: Acetylcholine Chloride for Injection)

3.14.2 Description of odor and taste

Odor and taste are not necessary to be described in principle, but describe them only when necessary to provide information to analysts. Do not describe odor and taste for drugs that can be harmful to the health of analysts such as poisonous and deleterious drugs, narcotic and psychotropic drugs, drugs with a strong effect, or those easy to disperse.

3.14.3 Color

Follow the expression of color by JIS Z 8102:2001 “Names of non-luminous object colors”.

3.14.3.1 Basic expression of chromatic colors

The basic names of chromatic colors are red, yellow-red, yellow, yellow-green, green, blue-green, blue, blue-purple, purple, and red-purple. In addition to these colors, brown, orange, and yellow-white can be used. The expression of a color comparing to something like brick-red, salmon, and violet should not be used in principle.

3.14.3.2 Basic expression of achromatic colors

The basic names of achromatic colors are white (including practically white), light gray, gray, dark gray, and black.

3.14.3.3 Brightness and saturation of chromatic colors

Express brightness and saturation of chromatic colors as very pale, pale, grayish, dark, very dark, and vivid. Deep, light and slight (faint) may be used. The expression of lightness and darkness is in the order of deep, light and slight.

[Example] Very pale red, dark red

Use reddish, yellowish, greenish, bluish and purplish as the adjectives indicating hue.

[Example] Bluish purple

3.14.3.4 Expression for colorless

The expression of colorless includes practically colorless. Describe 「無色澄明の液」(“clear, colorless liquid”) instead of 「無色の澄明の液」(“clear and colorless liquid”).

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3.14.4 Form

3.14.4.1 Crystals, crystalline powder, and powder

Use the following expression for crystals and powder.

Crystals — Confirmed as crystals by the observation with naked eye or a magnifying lens.

Powder — Described as “powder” if not confirmed as crystals by the observation with naked eye or a magnifying lens.

Crystalline powder — Among powders, the expression 「結晶性の粉末」in Japanese ("crystalline powder" in English) is acceptable if crystals are observed by the X-ray powder diffraction method or optical microscope. The term 「結晶性粉末」in Japanese should not be used.

3.14.5 Odor

3.14.5.1 Expression of odor

Describe odor according to the following expression.

Amine-like odor, irritative odor, characteristic odor, unpleasant odor, aromatic odor, AAA-like odor

3.14.5.2 Intensity of odor

Express the intensity of odor as follows.

Intense, strong, weak, slight, faint

3.14.6 Taste

3.14.6.1 Expression of taste

Describe taste by the following expression.

Sweet, pungent, saline taste, hot, acidic, salty, burning, astringent, bitter, bitter taste, warm sensation, cold sensation, metallic

3.14.6.2 Intensity of taste

Express the intensity of taste as follows.

Intense, strong, weak, slight, faint

3.14.7 Solubility

3.14.7.1 Sequence of description of solvents

In describing solubility, state solvents in descending order of solubility.

If the solubility is same, solvents are generally mentioned in the following order: water, formic acid, acetonitrile, *N*,*N*-dimethylformamide, methanol, ethanol (99.5) [or ethanol (95)], acetic anhydride, acetone, 2-propanol, 1-butanol, pyridine, tetrahydrofuran, acetic acid (100), ethyl acetate, diethyl ether, xylene, cyclohexane, hexane and petroleum ether. For solvents other than mentioned above, determine the order considering the polarity.

Attention should be paid to the rule under 1.2 for the use of a solvent and 7.2.3 for the name of a solvent.

3.14.7.2 Solvents to be specified solubility

The solvents used to determine the solubility are water and ethanol (99.5), and in principle, all the solvents used for tests as well. When ethanol (95) is used for the testing, specify the solubility in ethanol (95) instead of that in ethanol (99.5). When both ethanol (95) and ethanol (99.5) are used for the testing, specify the solubility in ethanol (99.5). The solvents used for tests are those employed in dissolving the sample directly. Composites and their components are not included in principle.

Include the solvents, however, even if not used for testing but shows solubility characteristic to the drug. In addition, if multiple acidic or alkaline test solutions are used for testing, describe the solubilities as follows for each of a typical acidic or alkaline test solution with a line feed next to the general description of solubility.

[Example] It dissolves in dilute hydrochloric acid and in ammonia TS.

The component solvent of the developing solvent for thin-layer chromatography and the solvent used as acid or alkali for extraction are out of scope for solubility description.

Even if a solvent is not stated clearly due to the abbreviated test method description, such as water determination, describe the solubility in the solvent used to dissolve the sample directly (i.e. methanol for dissolving a sample for water determination).

3.14.7.3 Meaning of “dissolve” and “miscible”

The description “dissolve” or “miscible” indicates that the drug dissolves in the solvent to form a clear solution or is miscible with the solvent in arbitrary proportion to form a clear mixture.

3.14.7.4 Testing method for solubility and definition of terms expressing solubility

Solubility is expressed in the terms indicated below.

Unless otherwise directed, solubility means the degree of dissolution of drug, previously powdered to pass through a No. 100 (150 μm) sieve, within 30 minutes, in a solvent at 20 ± 5°C, by vigorously shaking for 30 seconds each time at 5-minute intervals. If the volume of a solvent obtained by the test covers two measuring volumes, use the term of the solubility for larger volume.

Solubility can be calculated from the concentration of a saturated solution.

[Descriptive term]	[Volume of solvent required for dissolving 1 g or 1 mL of solute]
Very soluble	Less than 1 mL
Freely soluble	From 1 mL to less than 10 mL
Soluble	From 10 mL to less than 30 mL
Sparingly soluble	From 30 mL to less than 100 mL
Slightly soluble	From 100 mL to less than 1000 mL
Very slightly soluble	From 1000 mL to less than 10000 mL
Practically insoluble	10000 mL and over

3.14.7.5 Expression of solubility in case of dissolving with gas evolution or salt formation

If a drug dissolves with reaction, such as gas evolution or salt formation, state “AAA dissolves in BBB” on a separate line next to the general description of solubility.

3.14.8 Acidity or alkalinity

Express the acidity or alkalinity of a solution with pH. Generally describe as “Dissolve *X* g of AAA in *Y* mL of water: the pH of the solution is...” or “The pH of a solution of AAA in BBB (1 in 20) is …”

3.14.9 Physical and chemical properties

Generally describe the characteristics regarding the physical or chemical changes of a relevant drug, such as hygroscopicity, deliquescence, efflorescence, volatility, evaporability, solidifiability, coagulability, change by light, change in color, decomposition, precipitate formation and so on.

In order to clearly describe the changes caused by light, use the term “decompose” for the changes when degradation products are detected. Describe discoloration as “it is colored to AA (color)”. Do not describe as “it is gradually affected by light”.

[Example] “It is gradually colored to brown by light.”
“It is hygroscopic.”
“It deliquesces in the presence of moisture.”

When the general description criterion (moisture absorption exceeds 3% kept at 25°C/75% RH for 7 days) is not applicable to the hygroscopicity of the drug, this characteristic is not stated in the Characters section. However, state the hygroscopicity in the corresponding test item as necessary when it gives impact on performing tests.

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3.14.10 Specific physical and/or chemical values in Description

3.14.10.1 Handling of specific physical and/or chemical values in Description

Specific physical and/or chemical values provided in the Description section are given for informational purposes and should not be interpreted as indicators of pass/fail criteria. Therefore, rough values may be described.

3.14.10.2 Presentation of specific physical and/or chemical values in Description

The method for presenting specific physical and/or chemical values should, in principle, adhere to the guidelines described in 3.17. However, the expression “about *X* °C” is acceptable for a melting point.

For a decomposition point, describe it as “about *X* °C (with decomposition)”, and do not express it as a range, such as “*X* – *Y* °C (decomposition)”. In addition, when the melting or decomposition occurs with a range of 10°C or more, do not specify this range. Instead, submit the information on temperature by which these phenomena can be confirmed from the physical appearance.

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3.14.10.3 Description of salt of drug showing optical activity

Among the salts of drugs showing an optical activity, when the salt is composed of the ion pair of “pharmacologically active but optically inactive acid or base moiety” and “pharmacologically inactive but optically active acid or base moiety” and thus shows optical rotation, state the optical rotation in the Description section as specific physical and/or chemical values. (Example: Ifenprodil Tartrate)

3.14.10.4 Handling of drugs containing asymmetric carbon but showing no optical rotation (e.g. racemate)

When a drug has asymmetric carbon(s) but shows no optical rotation, such as a racemate, describe in the Description section “A solution of XXX (1 in *AA*) shows no optical rotation” (for solid) or “It shows no optical rotation” (for liquid).

3.14.10.5 Handling of optical rotation when there is a specification for enantiomers or diastereomers in Purity

When there is a specification for enantiomers or diastereomers in Purity, describe the optical rotation in the Description section.

3.14.10.6 Example of description regarding crystal polymorphism

When a drug shows crystal polymorphism, describe it as follows.

[Example] AAA shows crystal polymorphism.

3.15 Description of a crude drug

Describe the Description of a crude drug, in the order of characteristics of external appearance, length, diameter, color of the outer surface, characteristic elements of the outer surface, characteristics of each part, external appearance observed under a magnifying glass, characteristic elements obtained by cutting or breaking horizontally, etc., odor, taste, characteristic elements observed under a microscope, solubility, acidity or alkalinity of solution, etc.

However, do not specify the odor and taste with the materials potential to give an adverse effect on the health of analysts.

For color, odor, taste, solubility, and acidity or alkalinity of solution, follow 3.14 Description. In addition, when the crude drug has multiple origins, and the Description are different according to each origin, assign a number with a right parenthesis to each origin, and state the scientific name (without author name) or the crude drug name and the full text of the Description to each.

3.16 Identification

3.16.1 Setting of Identification

Identification is the test to identify a drug or an active ingredient(s) of a drug based upon its specific property.

For a drug substance (chemical) describe generally infrared spectrophotometry and ultraviolet-visible spectrophotometry, and if it is a salt, describe the identification of the salt. Concerning a preparation (chemicals), establish one or more identification

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tests for each preparation, paying attention to the influence of other drug substances and excipients. When the identification is performed by using the relative retention time of liquid chromatography in the Assay etc., it is desirable to set liquid chromatography under another condition simultaneously or set different methods in parallel.

3.16.2 Rationalization of Identification

When the identification of a drug is possible by methods other than those described in the Identification, such methods may be taken into consideration. It is possible to set those methods as the identification test as necessary. When the identification of the drug is carried out by the tests in other than the Identification, describe the purport in the item of the Identification. (Refer to 3.16.9 Identification by Chromatography.)

3.16.3 Test procedure for Identification

The identification tests may be performed generally by physicochemical methods (spectroscopy, chemical reaction and chromatography), biochemical methods and/or biological methods.

For a biological product, establish test methods using structural analysis and physical/chemical methods (peptide mapping, SDS polyacrylamide gel electrophoresis, etc.), immunochemical methods (Western blotting, etc.), biochemical methods (enzyme activity test, etc.) or biological methods (cell response test, etc.) based on molecular structural features and other characteristic properties. If peptide mapping method is used, it is not necessary to set Constituent amino acids.

3.16.3.1 Spectroscopy

Establish in principle infrared spectrophotometry and ultraviolet-visible spectrophotometry as spectroscopic identification. However, consider carefully the significance of applying such methods to polymerized high-molecular compounds and others. Consider nuclear magnetic resonance spectroscopy and near infrared spectrometry as appropriate.

3.16.3.2 Chemical reaction

Establish a method utilizing a chemical reaction when the method can specifically confirm the characteristics of the chemical structure, however, it is not necessary to establish one when the functional groups such as halogen and nitro can be clearly identified by the infrared absorption spectrum.

3.16.3.3 Chromatography

In addition to usual qualitative tests, ultraviolet-visible spectrophotometry, infrared spectrophotometry and nuclear magnetic resonance spectroscopy, identification tests using the identity of R_f values or retention times derived from chromatographic methods, such as thin-layer chromatography, liquid chromatography, etc. can be established.

The Identification using the chromatography is performed by comparing with the reference material. However, it does not necessarily apply to the crude drugs, etc.

3.16.3.4 Immunochemical, Biochemical and Biological method

For a biological product, the identification tests can be established according to their immunological, biochemical or biological characteristics, in addition to structure and physicochemical properties.

3.16.4 Sequence of items of Identification

The items of Identification are described in the following order: color reaction, precipitation, decomposition, derivatization, absorption spectra (ultraviolet, visible, and infrared), nuclear magnetic resonance spectrum, chromatography, specific reaction, cation, and anion. A decomposition followed by a subsequent reaction is categorized into decomposition.

For a biological product, the order is as follows: structure and physicochemical properties (peptide mapping or constituent amino acids, retention time of HPLC, mobility in SDS polyacrylamide gel electrophoresis/ capillary electrophoresis, etc.), immunochemical properties (reactivity of ELISA, reactivity and mobility on Western blotting, neutralizing activity, etc.), biochemical properties (enzyme activity, binding affinity, etc.) or biological properties (cellular response, etc.).

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3.16.5 Case that the Qualitative Tests of General Tests are used as the Identification

When the Qualitative Tests in the General Tests are applied, description should be as follows.

When the material conforms to all items specified in the Qualitative Tests for chloride, state "XXX responds to Qualitative Tests <*1.09*> for chloride".

When only a specific test among the prescribed tests is performed, state "XXX responds to Qualitative Tests <*1.09*> (1) for YYY".

When a qualitative test is specified, the ionic concentration in the test solution is generally 0.2 – 1%. For clearer determination, specify the concentration in principle, e.g. "A solution of XXX (1 in 100) responds to Qualitative Tests <*1.09*> for YYY".

When the objective salt is different, set the items separately such as (1) Sodium salt, (2) Phosphate.

[Example]

(1) A solution of XXX (1 in 10) responds to Qualitative Tests <*1.09*> for sodium salt.

(2) A solution of XXX (1 in 10) responds to Qualitative Tests <*1.09*> (1) and (3) for phosphate.

3.16.6 Identification by Ultraviolet-visible Spectrophotometry

Consider setting the methods to compare spectrum of a sample with Reference Spectrum or spectrum of Reference Standard. The wavelength of Reference Spectrum is 220 nm or higher, in principle. However, the wavelength for measurement is 210 nm or higher, in principle, for drafting to judge the necessity of stipulating it at a shorter wavelength (e.g., case where the spectrum is out of scale at about 230 nm because the scale has been adjusted against the absorbance of the maximum absorption at a longer wavelength). In principle specify by the wavelength at absorption maximum and do not adopt Reference Spectrum when applying this method to the identification of preparations.

When the absorption spectrum of a sample is measured by ultraviolet-visible spectrophotometry under the same condition for measuring the Reference Spectrum or the spectrum of Reference Standard and both spectra are compared, the identity is confirmed if the spectra exhibit similar intensities of absorption at the same wavelengths.

The description is generally "Determine the absorption spectrum of a solution of XXX in ethanol (95) (1 in *VV*) as directed under Ultraviolent-visible Spectrophotometry <*2.24*>, and compare the spectrum with the Reference Spectrum (or the spectrum of a solution of XXX RS prepared in the same manner as the sample solution): both spectra exhibit similar intensities of absorption at the same wavelengths."

When it is difficult to establish the method comparing with the Reference Spectrum, adopt a method by stipulating the wavelengths at absorption maxima. The standard for the wavelength range to be specified is generally 4 nm. Specify the wavelength range of absorption shoulder, if the shoulder is observed apparently, and the range may be around 10 nm. Do not specify wavelength at absorption minimum in principle.

3.16.7 Identification by Infrared Spectrophotometry

Judge the acceptance/rejection by comparison with the Reference Spectrum or the spectrum of the Reference Standard according to Infrared Spectrophotometry <*2.25*>. However, when a drug is a salt, note that salt exchange can be occurred between the drug and added potassium bromide or potassium chloride. In principle, when the disk method or the diffuse reflectance method is applied, potassium chloride is used for a hydrochloride sample. In the case of other salts, trial such as the paste method is needed. When the ATR method is applied, do not use Reference Spectrum in principle because of the difficulty of setting Reference Spectrum.

The description is generally "Determine the infrared absorption spectrum of XXX, previously dried, as directed in the ZZZ method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum (or the spectrum of previously dried XXX RS): both spectra exhibit similar intensities of absorption at the same wave numbers."

If the material shows polymorphism, generally add the description about pre-treatment for re-determination after the above-mentioned judgment description except that a crystalline form of drug substance is specified. "Being specified separately …" can be used only when it is difficult to prescribe concretely. If relatively simple prescription can be made with reference to the European Pharmacopoeia, etc., it is necessary to describe the reprocessing method.

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[Example] "If any difference appears between the spectra, dissolve XXX (each of XXX and XXX RS) in YYY (respectively), then evaporate YYY to dryness, and repeat the test on the dried residue."

When it is difficult to establish the method comparing with the Reference Spectrum for preparations due to the interference of excipients, specify the wave numbers by selecting the characteristic absorption bands to the active ingredient. Round the wave number not less than 2000 cm^{-1} to the 10.

[Example] "Determine the infrared absorption spectrum of XXX as directed in the liquid film method under Infrared Spectrophotometry <*2.25*>: it exhibits absorption at the wave numbers of about 2940 cm^{-1}, 2810 cm^{-1}, 2770 cm^{-1}, 1589 cm^{-1}, 1491 cm^{-1}, 1470 cm^{-1}, 1434 cm^{-1}, 1091 cm^{-1} and 1015 cm^{-1}." (Chlorpheniramine Maleate Powder)

Select absorption bands in a wide wavenumber region and specify the absorption bands which are the major bands in the spectrum and useful for identifying the structure of the active ingredient. In addition, the functional group which is characteristic in the structure should be assigned in principle.

3.16.8 Identification by Nuclear Magnetic Resonance Spectroscopy

In principle, specify the chemical shifts of the signals from the signal of the internal reference compound, the splitting pattern, and the ratio of the integrated intensity of each signal, and describe the magnitude of the magnetic field of the equipment as reference. However, when measured in the different magnitude of a magnetic field of the equipment, the multiplicities of signals may be observed to be different due to the difference in resolving power among instruments and the relative relation between the size of spin-spin coupling and the difference in resonance frequency of spin-spin coupled nuclei. Therefore, it is desirable to measure in a sufficiently strong magnetic field so that the apparent multiplicity does not depend on the magnitude of the magnetic field.

[Example] "Determine the ^{1}H spectrum of a solution of AAA in deuterated water for nuclear magnetic resonance spectroscopy as directed under Nuclear Magnetic Resonance Spectroscopy <*2.21*>, using sodium 3-trimethylsilylpropanesulfonate for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits a triplet signal A at around δ 1.2 ppm, a doublet signal B at around δ 6.8 ppm and a doublet signal C at around δ 7.3 ppm. The ratio of the integrated intensity of these signals, A:B:C is about 3:2:2." (When the concentration of the sample is *X* and the frequency is *XX* MHz.)

3.16.9 Identification by Chromatography

For thin-layer chromatography, generally specify that the R_f values, color or shape and the like of the principal spots obtained from the sample solution and standard solution prepared by using the reference material are the same. If a reference material for assay is established with the same specification as the monograph, use the reference material for assay as a reference material in the identification test. However, if the content specification of the reference material for assay is stricter than the monograph by an additional specification, do not use the reference material for assay, but use the monograph in principle.

For liquid chromatography, specify that the retention times of the active ingredient obtained from the sample solution and standard solution prepared by using the reference standard or reference material are the same, or that the peak shape of the component is unchanged after mixing the sample with an authentic specimen. However, the comparison with the standard solution prepared by using the drug substance is acceptable in the case of preparations. Furthermore, when the detector by which the finding on the chemical structure of the test component can also be obtained at the same time is used, more specific identification can be performed by conformity of the information on the chemical structure in addition to the identity of the retention time.

[Example] Dissolve 0.1 g each of Amikacin Sulfate and Amikacin Sulfate RS in 4 mL of water, and use these solutions as the sample solution and standard solution. Perform the test with these solutions as directed under Thin-layer chromatography <*2.03*>. Spot 2 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 water, ammonia water (28), methanol and tetrahydrofuran (1:1:1:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin-citric acid-acetic acid TS on the plate, and heat at 100 °C for 10 minutes: the principal spot obtained from the sample solution and the spot from the standard solution show a red-purple color and the same *R*f value. (Amikacin Sulfate)

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[Example] Perform the test with 20 µL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the conditions described in the Assay: the retention times of the principal peaks obtained from the sample solution and standard solution are the same.

[Example] Perform the test with 25 µL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions: the retention times of the principal peaks in the chromatograms obtained from the sample solution and standard solution are the same, and both adsorption 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.

Detector: A photodiode array detector (wavelength: 270 nm, spectrum range of measurement: 220 – 370 nm).

System suitability—

System performance: When the procedure is run with 25 µL of the standard solution under the above operating conditions (wavelength: 270 nm), the number of theoretical plates and the symmetry factor of the peak of AAA are not less than 5000 and not more than 1.5, respectively.

3.16.10 Identification for counter ion of salt

If a drug to be tested is a salt, establish the identification for the pharmacologically inactive counter ion. However, this is not required for preparations in principle.

3.16.11 Description of names of substances to be identified

Only in the case necessary to specify the substance to be identified (e.g., Iodine, Salicylic Acid and Phenol Spirit), its name is indicated in parentheses at the end of description.

3.17 Specific physical and/or chemical values

3.17.1 Setting of specific physical and/or chemical values

Specify the test items using the concrete name such as optical rotation and melting point necessary to set up as pass/fail criterion. The specific physical and/or chemical values include alcohol number, absorbance, congealing point, refractive index, osmotic pressure ratio, optical rotation, constituent amino acids, viscosity, pH, content ratio of the active principle, specific gravity, boiling point, melting point, acid value, saponification value, ester value, hydroxyl value, and iodide value. The description order of the items follows the order shown above. However, the specification of absorbance can be omitted when Identification includes Ultraviolet-visible Spectrophotometry. In principle, set the pH for the drug substance used for injections, but this is not necessary for non-ionic compounds.

For a biological product, the specific physical and/or chemical values include molecular weight, isoelectric point, constituent amino acids, composition ratio/contents of monosaccharides (neutral sugars, amino sugars and sialic acids), oligosaccharide profile (composition ratio of oligosaccharides), glycoform profile, charge profile, composition ratio/contents of product-related substances, specific activity, pH and so on.

The description follows the rules shown under 3.17.2 – 3.17.15. Describe the operation procedure when it is different from that specified in the General Tests.

3.17.1.1 Specific physical and/or chemical values of a preparation

For a preparation, select as appropriate the test items directly relevant to quality evaluation on stability, efficacy and safety of the preparations.

With regard to a preparation of which the relevant drug substance is not listed in JP, describe the specific physical and/or chemical values of the drug substance as needed.

When the osmotic pressure ratio and pH of the preparation which are specified in marketing authorization dossier are specified in JP, describe "Being specified separately ⋯." For hydrophilic ointments among Ointments, oil-in-water (O/W) type creams

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among Creams, cataplasms/gel patches among Patches, the specification of pH is required. However, the specification of pH is not required for these preparations that contain drug substances with no possibility of hydrolysis. For antibiotics, specify them only when the osmotic pressure ratio/pH is specified in the Part 4, Japanese Pharmaceutical Codex (JPC). Describe the osmotic pressure ratio generally as below. For the injections dissolved at the time of use, describe the preparation method of the sample solution. It is not necessary to specify them in principle in the case where it is not administered intramuscularly.

[Example]

Osmotic pressure ratio *<2.47>* 0.9 – 1.1

Osmotic pressure ratio *<2.47>* The osmotic pressure ratio of a solution prepared by dissolving an amount of XXX for Injection, equivalent to 1.0 g of "XXX", in 10 mL of water for injection is between 1.0 and 1.2.

3.17.2 Expression of absorbance

Describe absorbance generally as below. However, when the reference spectrum method under Ultraviolet-visible Spectrophotometry is specified for the identification test, the absorbance may not be specified as the specific physical and/or chemical value.

Absorbance *<2.24>* $E^{1\%}_{1\mathrm{cm}}$ (247 nm): 390 – 410 (after drying, 10 mg, methanol, 1000 mL).

This means "Dry XXX under the conditions specified in Loss on drying. Prepare the solution in the same proportion to that prepared by weighing accurately about 10 mg of the dried material on a microchemical balance and being dissolved in methanol to make exactly 1000 mL. Determine the absorbance of the solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*: $E^{1\%}_{1\mathrm{cm}}$ of the solution at a wavelength of 247 nm is between 390 and 410".

1% in the symbol for absorbance means 1 g/100 mL.

3.17.3 Expression of congealing point

Describe congealing point generally as follows.

Congealing point *<2.42>* Not less than 112°C.

This means "Perform the test with XXX as directed under Congealing Point Determination *<2.42>*: the congealing point is not less than 112°C".

3.17.4 Expression of refractive index

Describe refractive index generally as follows.

Refractive index *<2.45>* n^{20}_{D}: 1.481 – 1.486

This means, "Perform the test with XXX at 20°C as directed under Refractive Index Determination *<2.45>*: the refractive index, n^{20}_{D}, is between 1.481 and 1.486".

3.17.5 Expression of optical rotation

Describe optical rotation generally as follows.

Optical rotation *<2.49>* $[\alpha]^{20}_{\mathrm{D}}$: +48 – +57° (after drying, 0.25 g, water, 25 mL, 100 mm).

This means "Dry XXX under the conditions specified in Loss on drying, weigh accurately about 0.25 g of the material, dissolve in water to make exactly 25 mL. Perform the test with this solution at 20°C in a 100-mm cell as directed under Optical Rotation Determination *<2.49>*: the specific optical rotation, $[\alpha]^{20}_{\mathrm{D}}$, of this solution is between +48° and +57°".

3.17.6 Expression of viscosity

Describe viscosity generally as follows.

Viscosity *<2.53>* 345 – 445 mm^2/s (Method 1, 25°C).

This means "Perform the test with XXX at 25°C as directed under Method 1 of Viscosity Determination *<2.53>*: the kinematic viscosity of XXX is between 345 mm^2/s and 445 mm^2/s".

Viscosity *<2.53>* 123 – 456 mPa·s (Method 2, 20°C).

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This means “Perform the test with XXX at 20°C as directed under Method 2 of Viscosity Determination <*2.53*>: the viscosity of XXX is between 123 mPa·s and 456 mPa·s ”.

3.17.7 Expression of pH

Describe pH generally as follows.

For liquid drugs:

pH <*2.54*> 7.1 – 7.5

This means “Perform the test with XXX as directed under pH Determination <*2.54*>: the pH of XXX is between 7.1 and 7.5”.

For solid drugs:

pH <*2.54*> Dissolve 1.0 g of XXX in *VV* mL of AAA: the pH of the solution is between *YY* and *ZZ*.

3.17.8 Expression of specific gravity

The description of specific gravity is generally as follows.

Specific gravity <*2.56*> d_{20}^{20}: 0.718 – 0.721

This means “Perform the test with XXX at 20°C as directed under Determination of Specific Gravity and Density <*2.56*>: the specific gravity, d_{20}^{20}, of the sample is between 0.718 and 0.721.”

3.17.9 Expression of boiling point

The description of boiling point is generally as follows.

Boiling point <*2.57*> 118 – 122°C

This means “Perform the test with XXX as directed under Boiling Point and Distilling Range Test <*2.57*>: the boiling point of the sample is between 118°C and 122°C.”

3.17.10 Expression of melting point

The description of melting point is generally as follows.

Melting point <*2.60*> 110 – 114°C

This means “Perform the test with XXX as directed under Method 1 of Melting Point Determination <*2.60*>: the melting point of the sample is between 110°C and 114°C”.

When Method 2 or Method 3 is used, it should be noted after the figure of melting point.

[Example] Melting Point <*2.60*> 56 – 72°C (Method 2).

3.17.11 Expression of acid value

The description of acid value is generally as follows.

Acid value <*1.13*> 188 – 203

This means “Perform the test with XXX as directed under Fats and Fatty Oils Test <*1.13*>: the acid value of the sample is between 188 and 203”.

3.17.12 Expression of ester value (saponification value, hydroxyl value, etc.)

The description of ester value is generally as follows.

Ester value <*1.13*> 72 – 94

This means “Perform the test with XXX as directed under Fats and Fatty Oils Test <*1.13*>: the ester value of the sample is between 72 and 94”.

Describe saponification value and hydroxyl value in the manner similar to that of ester value.

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3.17.13 Expression of iodine value

The description of iodine value is generally as follows.

Iodine value <*1.13*> 18 – 36

This means "Perform the test with XXX as directed under Fats and Fatty Oils Test <*1.13*>: the iodine value of the sample is between 18 and 36".

3.17.14 Expression of constituent amino acid

When Amino Acid Analysis of Proteins in the General Tests is applied, describe the method of hydrolysis, the method of amino acid analysis, specification values, procedures of hydrolysis (specify in detail because there are modified methods such as a combination of plural methods, etc.) and amino acid analysis in this order.

However, since color developing solutions, etc. are often integrated with analysis equipment, detailed composition ratios and preparation methods of them are not necessarily specified.

[Example] Constituent amino acids of Celmoleukin (Genetical Recombination)

When hydrolyze Celmoleukin (Genetical Recombination) according to Method 1 and Method 4 described in "1. Hydrolysis of Protein and Peptide", and perform the test according to Method 1 described in "2. Methodologies of Amino Acid Analysis" under Amino Acid Analysis of Proteins <*2.04*>, the molar ratios of the respective amino acids are as follows: glutamic acid (or glutamine) is 17 or 18, threonine is 11 to 13, aspartic acid (or asparagine) is 11 or 12, lysine is 11, isoleucine is 7 or 8, serine is 6 to 9, phenylalanine is 6, alanine is 5, proline is 5 or 6, arginine is 4, methionine is 4, cysteine is 3 or 4, valine is 3 or 4, tyrosine is 3, histidine is 3, glycine is 2, and tryptophan is 1.

Procedure

(i) Hydrolysis Based on the results of the Assay (1), place an amount of Celmoleukin (Genetical Recombination), equivalent to about 50 µg as the total protein in two hydrolysis tubes, and evaporate to dryness under vacuum. To one of the hydrolysis tubes add 100 µL of a mixture of diluted hydrochloric acid (59 in 125), mercapto acetic acid and phenol (100:10:1), and shake. Place this hydrolysis tube in a vial and humidify the inside of the vial with 200 µL of the mixture of diluted hydrochloric acid (59 in 125), mercapto acetic acid and phenol (100:10:1). Replace the vial interior with inert gas or reduce the pressure, and heat at about 115°C for 24 hours. After drying under vacuum, dissolve in 0.5 mL of 0.02 mol/L hydrochloric acid TS, and use this solution as the sample solution (1). To the other hydrolysis tube, add 100 µL of ice-cold performic acid, oxidize for 1.5 hours on ice, add 50 µL of hydrobromic acid, and dry under vacuum. Add 200 µL of water, repeat the dry under vacuum procedure two more times, place the hydrolysis tube in a vial, and humidify the inside of the vial with 200 µL of diluted hydrochloric acid (59 in 125). Replace the vial interior with inert gas or reduce the pressure, and heat at about 115°C for 24 hours. After drying under vacuum, dissolve in 0.5 mL of 0.02 mol/L hydrochloric acid TS, and use this solution as the sample solution (2). Separately, weigh exactly 60 mg of L-aspartic acid, 100 mg of L-glutamic acid, 17 mg of L-alanine, 23 mg of L-methionine, 21 mg of L-tyrosine, 24 mg of L-histidine hydrochloride monohydrate, 58 mg of L-threonine, 22 mg of L-proline, 14 mg of L-cystine, 45 mg of L-isoleucine, 37 mg of L-phenylalanine, 32 mg of L-arginine hydrochloride, 32 mg of L-serine, 6 mg of glycine, 18 mg of L-valine, 109 mg of L-leucine, 76 mg of L-lysine hydrochloride and 8 mg of L-tryptophan, dissolve with 0.1 mol/L hydrochloric acid TS to make exactly 500 mL, and use this solution as the standard solution. Transfer 40 µL each of the standard solution to two hydrolysis tubes, evaporate to dryness under vacuum, and proceed in the same way for each respective sample solution to make the standard solutions (1) and (2).

(ii) Amino acid analysis Perform the test with exactly 250 µL each of the sample solutions (1) and (2) and standard solutions (1) and (2) as directed under Liquid Chromatography <*2.01*> according to the following conditions, and from the peak areas for each amino acid obtained from the sample solutions (1) and (2) and standard solutions (1) and (2) calculate the molar number of the amino acids contained in 1 mL of the sample solutions (1) and (2). Furthermore, calculate the number of amino acids assuming there are 22 leucine residues in one molecule of celmoleukin.

[Example]

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Operating conditions—

Detector: A visible absorption photometer [wavelengths: 440 nm (proline) and 570 nm (amino acids other than proline)].

Column: A stainless steel column 4 mm in inside diameter and 25 cm in length, packed with strongly acidic ion-exchange resin for liquid chromatography composed with sulfonated polystyrene (5 mm in particle diameter).

Column temperature: A constant temperature of about 57°C when the sample is injected. After a certain time, raise the temperature to a constant temperature of about 62°C.

Reaction temperature: A constant temperature of about 98°C.

Color developing time: Approximately 2 minutes.

Mobile phase: After preparing mobile phases A, B, and C according to the following table, add 0.1 mL of capric acid to each.

(Table is omitted)

Flowing of mobile phase: Control the gradient by mixing the mobile phases A, B, C and D as directed in the following table.

(Table is omitted)

Changing mobile phases and column temperature: When operating under the above conditions using 0.25 mL of the amino acid standard solution, the amino acids will elute in the following order; aspartic acid, threonine, serine, ⋯ and arginine. Switchover to the mobile phases A, B, and C, in sequence so that the resolution between the peaks of cystine and valine is 2.0 or more and that between ammonia and histidine is 1.5 or more. Also, increase the temperature after a constant length of time so that the resolution between the peaks of glutamic acid and proline is not less than 2.0.

Reaction reagents: Dissolve 408 g of lithium acetate dihydrate in water, and add 100 mL of acetic acid (100) and water to make 1000 mL. To this solution add 1200 mL of dimethylsulfoxide and 800 mL of 2-methoxyethanol. This solution is used as solution (I). Separately, mix together 600 mL of dimethylsulfoxide and 400 mL of 2-methoxyethanol and then add 80 g of ninhydrin and 0.15 g of sodium borohydride. This solution is used as solution (II). After gassing 3000 mL of the solution (I) for 20 minutes with nitrogen, rapidly add 1000 mL of the solution (II) and then mix by gassing for 10 minutes with nitrogen.

Mobile phase flow rate: About 0.275 mL per minute.

Reaction reagent flow rate: About 0.3 mL per minute.

System suitability—

System performance: When the procedure is run with 0.25 mL of the standard solution under the above operating conditions, the resolution between the peaks of threonine and serine is not less than 1.5.

3.17.15 Description of glycosylation analysis

When Glycosylation Analysis of Glycoprotein in the General Tests is applied, describe the method of glycosylation analysis, specifications and procedures in this order.

[Example 1] Monosaccharide composition (neutral sugars and amino sugars)

Monosaccharide composition (neutral sugars and amino sugars) Perform the test according to the monosaccharide composition (neutral sugars and amino sugars) under Glycosylation Analysis of Glycoprotein *<2.64>*: The contents of galactosamine, glucosamine, galactose, fucose and mannose per protein XXX are *XX* - *YY*, *ZZ* - *WW*, *VV* - *UU*, *TT* - *SS* and *RR* - *QQ*, respectively.

Weigh exactly an amount of AAA, equivalent to *X* µg as the total protein, desalt according to XX method, and dissolve in 100 µL of water. Transfer this solution to a hydrolysis tube (about 1.5 mL, made of glass or polypropylene), add 62 µL of trifluoroacetic acid, heat at 100°C for 4 hours, and evaporate to dryness under reduced pressure. To the residue add 200 µL of methanol, and evaporate to dryness under reduced pressure again. To the residue add exactly 10 µL of a solution of sodium acetate trihydrate (1 in 100) to dissolve, add exactly 50 µL of aminobenzoate derivatization TS, mix, and heat at 80°C for 30 minutes. Add exactly *Y* µL of the mobile phase A, and use this solution as the sample solution. Separately, dissolve 36.0 mg each of

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galactose, glucose and mannose, 44.2 mg each of galactosamine and glucosamine, and 32.8 mg of fucose in water to make exactly 100 mL, respectively. Pipet Z mL, W mL, V mL, U mL, T mL and S mL of these solutions, mix, add water to make exactly 10 mL, and use this solution as the monosaccharide mixed standard stock solution. Proceed with 100 μL each of this solution and water in the same manner as the sample solution, and use these solutions as the monosaccharide mixed standard solution and the blank solution. Perform the test with exactly R μL each of the sample solutions, monosaccharide mixed standard solution and blank solution as directed under Liquid chromatography <*2.01*> according to the following conditions. Determine the content of each monosaccharide from the peak area of each monosaccharide.

[Example 2] Monosaccharide composition (sialic acids)

Monosaccharide composition (sialic acids) Perform the test according to the monosaccharide composition (sialic acid) under Glycosylation Analysis of Glycoprotein <*2.64*>: The contents of *N*-acetylneuraminic acid and *N*- glycolylneuraminic acid per protein XXX are XX -YY and ZZ - WW, respectively.

Desalt an amount of AAA, equivalent to X μg as the total protein, according to XX method, and dissolve in 50 μL of water. To this solution add exactly 50 μL of 0.1 mol/L hydrochloric acid TS, mix, heat at 80°C for 1 hour, cool in ice water, and use this solution as the sample solution. Separately, dissolve each 15.5 mg of *N*-acetylneuraminic acid and 16.3 mg of *N*-glycolylneuraminic acid in water to make exactly 5 mL, respectively. Pipet Y μL and Z μL of these solutions, mix, add water to make exactly 10 mL, and use this solution as the sialic acid standard stock solution (1). Pipet XX μL of the sialic acid standard stock solution (1), add water to make exactly 10 mL, and use this solution as the sialic acid standard stock solution (2). Pipet 50 μL each of the sialic acid standard stock solutions (1), (2) and water, add exactly 50 μL of 0.1 mol/L hydrochloric acid TS to each, and use these solutions as the sialic acid standard solution (1), the sialic acid standard solution (2) and the blank solution. To the sample solution, the sialic acid standard solutions (1), (2) and the blank solution add exactly 200 μL of 1,2-diamino-4,5-methylenedioxybenzene derivatization TS to each, and mix. Heat them at 60°C for 2 hours protecting from light, and cool in ice water to stop the reaction. Add exactly YY μL of water to each solution, and mix. Perform the test with exactly ZZ μL each of these solutions as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the content of each sialic acid.

[Example 3] Oligosaccharide profile

Oligosaccharide profile Perform the test according to the oligosaccharide profile under Glycosylation Analysis of Glycoprotein <*2.64*>: The chromatograms obtained from the sample solution and standard solution are the same, and the area percentages of peaks 1, 2, 3 and 4 are XA - XB%, XC - XD%, XE - XF% and XG - XH%, respectively.

Desalt an amount of AAA, equivalent to X μg as the total protein, according to XX method, and dissolve in water to make a solution so that each mL contains about 10 μg of the total protein. To 10 μL of this solution add 30 μL of water, 5 μL of 0.2 mol/L phosphate buffer solution (pH 7.2) and 5 μL of PNGase F TS, and react at 37°C for 16 hours. Purify the released oligosaccharides by carbon solid phase extraction, and evaporate to dryness under reduced pressure. To the residue add 10 μL of 2-aminobenzamide derivatization TS, mix and heat at 65°C for 3 hours. After the completion of the reaction add 1 mL of acetone, and mix thoroughly. Centrifuge at 15,000 rpm for 10 minutes, and remove the upper layer. Repeat this procedure 2 times. Dissolve the residue in 50 μL of a mixture of water and acetonitrile (1:1), and use this solution as the sample solution. Separately, proceed with XXX (reference material) in the same manner, and use this solution as the standard solution. Perform the test exactly with Y μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions.

3.18 Purity

3.18.1 Setting of Purity

The Purity are intended to specify the purity of drugs together with the other test items, and to prescribe test procedures to determine the kinds, limits and amounts of contaminants in drugs. The contaminants to be tested by the Purity are anticipated to

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be contaminated during manufacturing processes (including raw materials and solvents) or to be generated during storage. Specify the related substances in principle. However, the specification of this item can be omitted if justified.

The impurities of biological products are classified into product-related impurities (for example, desamido substance, polymer, etc.) and process related impurities (host cell proteins, etc.) depending on its origin. For impurities that should be controlled, establish purity tests to judge the acceptance/rejection by limits. In case that purity tests are not established for those impurities, describe manufacture (except infectious substances).

Consider the test procedure with a small portion of sample for drugs with very small dosage. The test item can be omitted as long as it has no detrimental effect on the quality evaluation.

3.18.2 Order of items of Purity

The items of the Purity Tests should be put in the following order in principle.

Color, odor, clarity and/or color of solution, acidity or alkalinity, acid, alkali, chloride, sulfate, sulfite, nitrate, nitrite, carbonate, bromide, iodide, soluble halide, cyanide, selenium, cationic salt, ammonium, heavy metal, iron, manganese, chromium, bismuth, tin, aluminum, zinc, cadmium, mercury, copper, lead, silver, alkaline earth metals, arsenic, free phosphoric acid, foreign matter, related substances (related substances having safety concern, other related substances), isomer, enantiomer, diastereomer, polymer, residual solvent, other contaminants, residue on evaporation, and readily carbonizable substances.

3.18.3 Clarity and color of solution

Establish clarity and color of solution as needed especially if information on purity is obtained. Even if a drug substance is used for injections, it is not necessary to establish when the information on the purity cannot be obtained.

Use water as solvent, but if sufficient testing concentration is not secured due to the poor solubility, organic solvent, such as methanol, can be employed.

Specify clarity and color of solution by the comparison of absorbance values, by the comparison with matching fluids for color (Methods for Color Matching) and so on. When clarity and color of solution is specified according to General Notices 28, do not describe the number of a general test. Describe <*2.61*> only when compared with a standard solution by the judgment method of Turbidity Measurement <*2.61*>. Regarding to colorless, do not describe the number of a general test when specified according to General Notices 28, and describe <*2.65*> when judged by Methods for Color Matching <*2.65*>.

[Example 1] Clarity and color of solution Dissolve 0.8 g of AAA in 10 mL of water: the solution is clear and colorless.

[Example 2] Clarity and color of solution Dissolve 0.8 g of AAA in 10 mL of water: the solution is colorless. Perform the test with this solution as directed under Turbidity Measurement <*2.61*>: the solution is clear.

[Example 3] Clarity and color of solution Dissolve 0.8 g of AAA in 10 mL of water. Perform the test with this solution as directed under Turbidity Measurement <*2.61*>: the solution is clear. Perform the test with this solution according to Method 1 under Methods for Color Matching <*2.65*>: the solution is colorless.

When compared with matching fluids for color, do not describe the concrete color of the solution. Describe “Matching Fluid for Color” when compared with matching fluids for color A to T, and describe “Matching Fluid” when compared with a series of matching fluids (B series, BY series, etc.).

[Example 1] Clarity and color of solution Dissolve 1.0 g of AAA in 10 mL of water: the solution is clear. Perform the test with this solution as directed under Methods for Color Matching <*2.65*>: the solution is not more colored than Matching Fluid for Color M.

[Example 2] Clarity and color of solution Dissolve 0.8 g of AAA in 10 mL of water: the solution is clear. Perform the test with this solution according to Method 1 under Methods for Color Matching <*2.65*>: the solution is not more colored than Matching Fluid R4.

[Example 3] Clarity and color of solution Dissolve 0.8 g of AAA in 10 mL of water. Perform the test with this solution as directed under Turbidity Measurement <*2.61*>: the solution has no more turbidity than Reference suspension II. Perform the test with this solution according to Method 1 under Methods for Color Matching <*2.65*>: the solution is not more colored than Matching Fluid BY3.

In the test for clarity and color of solution, the standard concentration of the solution is 10 g/100 mL, namely (1 in 10). Determine the reasonable concentration based on the clinical dose concentration if it is higher than this concentration. In

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addition, choose the soluble highest concentration if the test is difficult to perform at the concentration of (1 in 10) due to the low solubility of the drug.

3.18.4 Inorganic salts, heavy metals and arsenic

Convert values obtained in the Purity for chloride, sulfate, heavy metals and arsenic into % or ppm referring to the Attached Table or according to the method conforming to it. The amount of a sample to be taken is in accordance with the Attached Table.

3.18.4.1 Specification of inorganic salts, heavy metals, arsenic, etc.

Specify inorganic salts, heavy metals, arsenic, etc. in consideration of the manufacturing processes (including raw materials and solvents) and the administration and dosage.

For a crude drug, specify them also in consideration of natural contents, etc. in the source animal, plant and minerals.

[Example] Heavy metals <*1.07*> Proceed with 2.0 g of XXX 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).

[Example] Arsenic <*1.11*> Prepare the test solution with 1.0 g of XXX according to Method 3, and perform the test (not more than 2 ppm).

3.18.4.2 Chloride and sulfate

In the tests for chloride and sulfate, prepare the test solutions in principle after dissolving samples in appropriate solvent.

[Example] Chloride <*1.03*> Perform the test with 2.0 g of XXX. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.007%).

[Example] Sulfate <*1.14*> Perform the test with 2.0 g of XXX. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (not more than 0.010%).

3.18.4.3 Soluble halide

Specify soluble halide when testing halogen other than chlorine.

3.18.4.4 Principle of setting the test for arsenic

Specify arsenic in either of the following cases. However, when arsenic is not specified in the marketing authorization dossier as specification, it is not necessary to specify except for crude drugs.

(1) Possible arsenic contamination in the manufacturing process
(2) Compounds containing phosphoric acid (phosphates, phosphoric esters, etc.)
(3) Inorganic compounds

3.18.4.5 Spike-recovery rate for arsenic and heavy metals

Investigate in advance the spike-recovery rate for arsenic and heavy metals.

Perform a spike-recovery test at the concentration level of the specification value in principle, and the recovery rate must be not less than 70%.

3.18.5 Related substances

3.18.5.1 Principle of setting the related substances test

For the related substances that have safety concern, establish a highly specific test method which can determine their individual amount accurately. For the related substances whose structures are required to be specified, establish a highly specific test method which can determine accurately the individual amounts, even if they are small amounts.

For the related substances tests that are specified by indicating the relative retention times as an individual peak in a monograph (except crude drugs), show the names and the structural formulas of the related substances in the “Others” of the monograph in principle. The chemical names in English prepared according to IUPAC nomenclature system are used for the names of related substances. For structurally unknown related substances among related substances that should be specified as the individual peaks, describe them as “structurally unknown substance having the relative retention time of about *T*” and describe the summary of unsuccessful studies for structure determination in the template 4.

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The alternative method (second method) of a test method can be established only when existing test methods cannot be applied because of a different impurity profile due to difference in manufacturing processes. In the meantime, conditions under which alternative method (second method) can be established are limited to satisfy the following: ① drug substance, ② purity test (related substances) is considered to be difficult to control uniformly because of a different impurity profile due to difference in manufacturing processes, ③ a newly listed draft is submitted after the Guideline for drafting The Japanese Pharmacopoeia, Seventeenth Edition (partial revision 2) (October 5, 2015) is released, ④ setting using the reference standard of a related substance, in principle.

For a preparation, an alternative method (second method) is not allowed in the meantime, but an alternative method (second method) can be established as well as a drug substance only when using the same reference standard of the related substance as the drug substance.

[Example 1] Standard description (related substances)

Others
Related substance A: Name
Structural formula
Related substance B: Name
Structural formula
Related substance C: Name
Structural formula

[Example 2] Standard description when an alternative method (second method) is added

Related substances Perform the test by one of the following methods according to the manufacturing processes.

1) Method 1 Weigh accurately …
2) Method 2 Weigh accurately …

[Example 3] Standard description when alternative methods (second and third methods) is added in addition to the established purity tests (related substances 1 and 2)

Related substances Perform the test by one of the following methods according to the manufacturing processes.

1) Method 1
Related substance 1 Weigh accurately …
Related substance 2 Weigh accurately …
2) Method 2
Related substance 1 Weigh accurately …
Related substance 2 Weigh accurately …
3) Method 3
Related substance Weigh accurately …

3.18.5.2 Degradation products

In consideration of findings about manufacturing processes, forced degradation products and stability study results, establish the test for the contaminants due to the degradation during manufacturing process and storage as necessary.

Consider the test for related substances when the degradation products are generated newly or increase significantly during the storage of preparations.

3.18.5.3 Test procedure for related substances

Establish the test procedure for related substances in view of quantitative capability and detection sensitivity.

For liquid chromatography, use a diluted sample solution or a solution prepared using the reference standard of an active ingredient or a related substance and so on as the standard solution. When the quantifiability of the related substances can be confirmed to around 0.1%, the area percentage method can also be used. The reference standard of a related substance can be used as a reference standard for system suitability to identify peaks and confirm separation. When using the standard material of a related substance besides the reference standard of a related substance, use the standard material which is generally available and has the quality appropriate for the purpose of testing.

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For thin-layer chromatography, employ the test procedure to compare with spots obtained from the standard solution and do not use the judgment “it gives a single spot”. As the standard solution use the diluted solution(s) of the sample solution to the acceptance limit or the solution of the standard material of the related substance(s).

3.18.5.4 Concept of setting limit of related substances

Specify the limit of the related substance which has safety concern by a percentage to the sample amount or a comparison with a standard solution.

For related substances, specify both limits of their individual and total amount by an area percentage method or comparison with a standard solution.

However, in the case where the limit of individual related substance is specified as not more than 0.2% by thin-layer chromatography and as not more than 0.1% by liquid chromatography, etc., the total related substances may not be specified. When the total limit is specified in addition to the individual limit of not more than 0.1% as shown the above, specify the test for required detectability in principle at 0.05% or below.

[Example 1] Standard description;

Dissolve *W* mg of XXX in *V* mL of SSS, and use this solution as the sample solution. Pipet *B* mL of the sample solution, add the mobile phase to make exactly *C* mL, and use this solution as the standard solution. Perform the test with exactly *D* µL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the conditions described below. Determine each peak area by the automatic integration method: the peak area of related substance A, having the relative retention time of about *E* to AAA obtained from the sample solution is not larger than *F* times the peak area of AAA from the standard solution, the peak area of related substance B, having the relative retention time of about *G* from the sample solution is not larger than *H* times the peak area of AAA from the standard solution, and the area of any peak other than AAA and the peaks mentioned above from the sample solution is not larger than the peak area of AAA from the standard solution. In addition, the total area of the peaks other than AAA from the sample solution is not larger than *I* times the peak area of AAA from the standard solution. For the areas of related substances, A and B, multiply their correction factors, *XX* and *YY*, respectively (in the case where the correction factors are described).

[Example 2] Description using area percentage method;

Dissolve *X* mg of XXX in *Y* mL of XX, and use this solution as the sample solution. Perform the test with *Z* µL of the sample solution as directed under Liquid Chromatography *<2.01>* according to the conditions described below. Determine each peak area by the automatic integration method, and calculate the amount of them by the area percentage method: the amount of related substances A, B, C and D, having the relative retention times of about *RA*, about *RB*, about *RC* and about *RD* to AAA, are not more than *M*%, respectively, the amount of related substance E, having the relative retention time of about *RE*, is not more than *N*%, the amount of related substance F, having the relative retention time of about *RF*, is not more than *P*%, and the amount of the peak other than AAA and the peaks mentioned above is not more than *Q*%. The total amount of the peaks other than AAA and related substance E is not more than *R*%.

[Example 3] Description using the reference standards of related substances

Weigh accurately about *X* mg of AAA, dissolve in the mobile phase to make exactly *Y* mL, and use this solution as the sample solution. Separately, weigh accurately about *Z* mg each of AAA Related Substance A RS, AAA Related Substance B RS and AAA RS, and dissolve them in the mobile phase to make exactly *W* mL. Pipet *V* mL of this solution, and add the mobile phase to make exactly *U* mL. Pipet *T* mL of this solution, add the mobile phase to make exactly *S* mL, and use this solution as the standard solution. Perform the test with exactly *R* µL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the conditions described below. Determine the peak areas A_{T1} and A_{T2}, of related substances A and B, having the relative retention times of about *RA* and about *RB* to AAA, the total area, A_{T3}, of peaks of other related substances, obtained from the sample solution, and then the peak areas A_{S1}, A_{S2} and A_{S3}, of related substances A and B, and AAA from the standard solution by the automatic integration method, and calculate the amount of related substances by the following equations: related substances A, B and the total amount of other related substances are not more than *XX*%, *YY*% and *ZZ*%, respectively. For the areas of related

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substances C and D, having the relative retention time of about *RC* and about *RD* to AAA, multiply their correction factors, *FC* and *FD*, respectively (when the correction factors are described).

Amount (%) of related substance A = $M_{S1} / M_T \times A_{T1} / A_{S1} \times CA$
Amount (%) of related substance B = $M_{S2} / M_T \times A_{T1} / A_{S2} \times CB$
Total amount (%) of other related substances = $M_{S3} / M_T \times A_{T3} / A_{S3} \times CT$

M_{S1}: Amount (mg) of AAA Related Substance A RS taken
M_{S2}: Amount (mg) of AAA Related Substance B RS taken
M_{S3}: Amount (mg) of AAA RS taken
M_T: Amount (mg) of AAA taken

[Example 4] Description when using the reference standard of an active ingredient

Weigh accurately about *X* mg of AAA, dissolve in the mobile phase to make exactly *Y* mL, and use this solution as the sample solution. Separately, weigh accurately about *Z* mg of AAA RS, dissolve in the mobile phase to make exactly *W* mL. Pipet *V* mL of this solution, and add the mobile phase to make exactly *U* mL. Pipet *T* mL of this solution, add the mobile phase to make exactly *S* mL, and use this solution as the standard solution. Perform the test with exactly *R* μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the conditions described below. Determine the peak areas, A_{T1} and A_{T2}, of related substances A and B, having the relative retention times of about *RA* and about *RB* to AAA, and total area, A_{T3}, of peaks of other related substances, obtained from the sample solution, and the peak area, A_S, of AAA from the standard solution by the automatic integration method, and calculate the amount of related substances by the following equations: the amounts of related substances A, B and the total amount of the other related substances are not more than *XX*%, *YY*% and *ZZ*%, respectively. For the areas of related substances, A and B, multiply their correction factors, *FA* and *FB*, respectively (when the correction factors are described).

Amount (%) of related substance A = $M_S / M \times A_{T1} / A_S \times CA$
Amount (%) of related substance B = $M_S / M \times A_{T2} / A_S \times CB$
Total amount (%) of other related substances = $M_S / M_T \times A_{T3} / A_S \times CT$
M_S: Amount (mg) of AAA RS taken
M_T: Amount (mg) of AAA taken

3.18.5.5 Use of correction factor (response factor) for related substances

The response factor is the ratio of the response of a certain substance to that of a reference material from the detector, and correction is performed by multiplying the peak areas of related substances by the correction factor, which is the reciprocal of the response factor. For related substances test, the correction factors indicated in each monograph are always applied. Correct a peak area when its response factor exceeds the range of 0.8 to 1.2. Correction may also be made, if deemed desirable, even when the response factor does not exceed the range of 0.8 to 1.2. Specifically, describe that the peak area obtained by automatic integration method is multiplied by the correction factor. In principle, the digit number of a correction factor is one decimal place.

3.18.5.6 Order of description of related substances

In principle, the specification of related substances is described in the ascending order of relative retention time.

In monographs (except crude drugs), related substances specified by indicating their relative retention times as individual peaks are attached with alphabets (related substance A, related substance B, ⋯) in the ascending order of relative retention time. Alphabets which correspond to the notation of a foreign pharmacopoeia or the like may be selected exceptionally.

With setting an alternative method (second method), the related substances with known structures which are newly shown are attached with alphabets following the number used previously in the ascending order of relative retention time.

When a related substance in the monograph of a drug product is the same with that in the monograph of the drug substance, attach the same alphabet and describe its correspondence in “Others” of the monograph. In principle, the other related substances

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in the monograph of a drug product are attached with two alphabets (related substance TA, related substance TB···) that are the combination of alphabets showing a formular type ("T" for tablets, "I" for injections, etc.) and the ascending order of relative retention time.

[Example 1] Standard rule for attaching alphabets in the monograph of a drug substance

Related substance A, B, C, D (Attach alphabets in the ascending order of relative retention time.)

[Example 2] Standard description when an alternative method (second method) is established

1) Method 1 Related substance A, B, C, D (Attach alphabets in the ascending order of relative retention time.)

2) Method 2 Related substance E, B, C, F (When new related substances E and F not established in the Method 1 are shown, attach alphabets in the ascending order of relative retention time.)

[Example 3] Standard description in the monograph of a drug product

Others

Related substances A and B: Refer to them described in AAA.

Related substance TA: Name

Structural formula

Related substance TB: Name

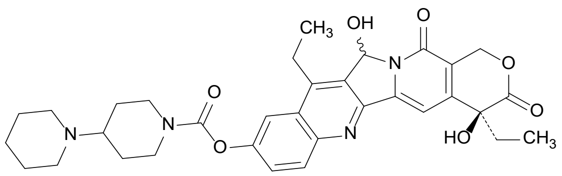
Structural formula

3.18.5.7 Description of structural formula and chemical name of related substances

Prepare the structural formula and chemical name of a related substance with reference to "3.6 Structural formula" and "3.8.1 Description of chemical names". If the stereochemistry has not been determined, the structure of the concerned part is indicated by a wavy line, and the hydrogen bonded to the carbon concerned is not described (unless essential for indicating the structure) (Example: Related substance A of Irinotecan Hydrochloride). Chemical names do not mention distinction between *R*-isomer and *S*-isomer or *E*-isomer and *Z*-isomer.

[Example]

Related substance A of Irinotecan Hydrochloride



(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

3.18.6 Residual solvents

Provide the information on the residual solvents (analytical methods, actual measurement data, etc.) in the case where organic solvents are used in the manufacturing processes. However, if it is necessary to specify limits different from those specified in Residual Solvents <*2.46*>, specify them as the individual contaminant in the monograph.

3.18.7 Residual monomer

For a polymeric compound manufactured by polymerization, establish the test for residual monomer as an item of the Purity.

3.18.8 Sampling

3.18.8.1 Drying of sample

In the Purity, generally use the sample as is without drying.

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3.18.8.2 Sampling amount

The sample amount for the Purity is generally as follows:
For mass, 0.10, 0.20, 0.30, 0.40, 0.5 – 3.0 g, etc.
For volume, 1.0, 2.0, 3.0, 4.0, 5 – 10 mL, etc.

When the final judgment is made as absolute mass, the sample must be weighed accurately, and significant figures should be considered in such case.

3.18.9 Description of the Purity proceeding as directed in the Assay

When specifying the liquid chromatography whose operating conditions are common to the Purity and the Assay, describe the operating conditions in the Assay and describe as the following example in the Purity.

[Example]

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 *XX* times as long as the retention time of YY, beginning after the solvent peak.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Pipet 1 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of XXX obtained with *V* μL of this solution is equivalent to 7 to 13% of that obtained with *V* μL of the standard solution.

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

3.18.10 Purity test for a preparation

Set the purity test for a preparation to determine contaminants that are especially desirable to be specified.

When the changes such as degradation occur during manufacturing process and storage of preparation, establish a test method which specify the kinds of the degradation products and their amounts or limits to secure safety based on the stability study results, etc. taking into consideration the dosage and administration of the drug and toxicity and pharmacological effects of the contaminants. In case for the formation of degradation products, attach the supporting data to justify the acceptance criterion.

3.19 Intentional adulteration

If there is a report of a drug intentionally contaminated with harmful substances, describe the control requirement as necessary. When describing the concrete test procedures of adulterated substances, follow the guidance provided in 3.18 Purity.

[Example] Control so that the contamination of AAA with XXX is within the specified limit. When the contamination is evaluated in release testing, perform the following test.

[Item name] When performing the purity test (1), the area of the peak having the relative retention time of about *XX* to ZZZ obtained from the sample solution is not larger than *YY* times the peak area of XXX from the standard solution.

3.20 Loss on drying, Water or Loss on ignition

3.20.1 Setting of Loss on drying and/or Water

When Loss on drying is selected, confirm that the sample does not decompose under the conditions of drying. (Establish the drying conditions which enable the dried sample to be used in other tests.) In the case where the dried sample is significantly hygroscopic, provide, for example, instructions to avoid moisture absorption. in each testing operation.

Select Water, in principle, when a drug decomposes under the drying conditions.

Select Water, in principle, for hydrates and set the specification values in range.

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Consider the test procedure with a small portion of sample for drugs with very small dosage. The test item can be omitted if the omission has no detrimental effect on the quality evaluation.

3.20.2 Loss on drying

3.20.2.1 Test for Loss on drying

Loss on drying is a method to determine the amount of water, all or a part of crystal water, or volatile substances in the drug which is removed during the drying. Perform the test according to Loss on Drying Test or Thermogravimetry under Thermal Analysis. For crude drugs, perform the test according to Loss on drying under Crude Drugs Test.

3.20.2.2 Description of Loss on drying

Describe Loss on drying as follows. Describe the specification value by loss on drying referring to the Attached Table (Percentage description for loss on drying and residue on ignition).

[Example] Loss on drying *<2.41>* Not more than 0.5% (1g, 105°C, 3 hours).

This indicates, “Weigh accurately about 1 g of the sample, put in a desiccator and dry at 105°C for 3 hours: the loss in mass is not more than 0.5%.”

[Example] Loss on drying *<2.41>* Not more than 4.0% (0.5 g, in vacuum, phosphorus (V) oxide, 110°C, 4 hours).

This indicates, “Weigh accurately about 0.5 g of the sample, put in a desiccator with phosphorus (V) oxide as the desiccant, and dry at 110°C under a reduced pressure of 2.0 kPa or lower for 4 hours: the loss in mass is not more than 4.0%.”

3.20.2.3 Description of Thermogravimetry under Thermal Analysis

Describe as follows when specified by Thermogravimetry under Thermal Analysis.

[Example] Loss on drying Perform the test with about *W* mg of XXX as directed in thermogravimetry under Thermal Analysis *<2.52>*according to the following conditions: not more than *YY* %.

Operating Conditions—

Heating rate: 5 °C per minute.
Temperature range: room temperature to 200 °C.
Atmospheric gas: dried Nitrogen.
Flow rate of atmospheric gas: 40 mL per minute.

Set the specification value to one decimal place.

3.20.3 Water

3.20.3.1 Water determination

The water determination is a method to determine water content in drugs and is performed according to Water Determination (Karl Fischer Method). When the sample amount is restricted, consider adopting coulometric titration since its limit of quantitation is lower when compared with that for volumetric titration.

3.20.3.2 Description of the Water

Describe the Water as follows, and indicate which method, volumetric titration (direct titration or back titration) or coulometric titration, is used.

[Example] Water *<2.48>* 4.0 – 5.5% (0.2 g, volumetric titration, direct titration).

This indicates, “Weigh accurately about 0.2 g of XXX, determine water by direct titration of volumetric titration as directed under Water Determination *<2.48>*. Water content of XXX is between 4.0% and 5.5%”.

When the description was simplified as above, describe the solubility in the solvent used for dissolving the sample in the Description.

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3.20.4 Loss on ignition

3.20.4.1 Test for the Loss on ignition

Loss on ignition is applied to inorganic drugs that lose a part of the components or contaminants during ignition. This test determines the loss in mass when the sample is ignited. Conduct the test according to Loss on Ignition Test.

3.20.4.2 Description of the Loss on ignition

Describe the Loss on ignition as follows.

[Example] Loss on ignition <*2.43*> Not more than 12.0% (1 g, 850 – 900°C, constant mass).

This indicates, "Weigh accurately about 1 g of XXX, ignite it at 850 – 900°C to constant mass. The loss in mass is not more than 12.0%."

3.20.5 Setting of the Loss on drying, the Water and the Loss on ignition for a preparation

Specify the Loss on drying, the Loss on ignition, and the Water for a preparation when particularly necessary. For example, if water content of a preparation affects its quality, specify it referring to that for the drug substance.

3.21 Residue on ignition, Total ash or Acid-insoluble ash

3.21.1 Setting of the Residue on ignition, the Total ash or the Acid-insoluble ash

Specify the Residue on ignition when the contents of inorganic substances contained as impurities in an organic substance, the amounts of inorganic substances contained as components of an organic substance, or the amounts of impurities contained in an inorganic substance which is volatilized on ignition are necessary to be specified. This is not necessary to be specified for metallic salt in principle.

Consider the test procedure with small sample quantity for drugs with very small dosage. The test item can be omitted if it has no detrimental effect on the quality evaluation.

Total ash is the residue of a crude drug when ignited as is. Acid-insoluble ash is the residue of ignited insoluble substance obtained by boiling a crude drug with dilute hydrochloric acid. Specify these for crude drugs as needed.

3.21.2 Description of Residue on ignition, Total ash or Acid-insoluble ash

Residue on ignition, Total ash or Acid-insoluble ash should be described as follows. Refer to the Attached Table (% Description for Loss on drying and Residue on ignition) for the expression of Residue on ignition in %. Express the ignition temperature in a range, such as "S – T°C", instead of "T°C".

[Example] Residue on ignition <*2.44*> Not more than 0.1% (1 g).

This means, "Weigh accurately about 1 g of XXX, and determine Residue on ignition as directed under Residue on Ignition Test <*2.44*>. Residue on ignition of XXX is not more than 0.1%."

[Example] Total ash <*5.01*> Not more than 5.0%.

This means, "Determine Total ash of XXX as directed under the Crude Drug Test <*5.01*>. Total ash of XXX is not more than 5.0%."

[Example] Acid-insoluble ash <*5.01*> Not more than 3.0%.

This means, "Determine Acid-insoluble ash of XXX as directed under the Crude Drug Test <*5.01*>. Acid-insoluble ash of XXX is not more than 3.0%."

3.22 Tests for preparations

3.22.1 Setting of tests for preparations

Establish the tests directed under the General Rules for Preparations and test items characterizing the attribute or function of a preparation. The principles for establishing the tests for preparations are shown below.

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3.22.1.1 Setting of tests stipulated in the General Rules for Preparations

When it is stipulated in the [3] Monographs for Preparations of the General Rules for Preparations that the preparation meets the requirements for General Tests, prescribe the tests concerned.

When it is stipulated as "AAA have an appropriate XX" in the [3] Monographs for Preparations of the General Rules for Preparations, investigate the establishment of the test regarding the preparation characteristic of "appropriate XX" by referring to "Specifications and Test Methods of New Pharmaceuticals" (PMSB/ELD Notification No. 568 dated May 1, 2001) and approved specifications, test methods, etc. However, among the preparation characteristics stipulated as "appropriate XX", it is not necessary to establish the item that has not been prescribed in the marketing authorization dossier.

Preparation characteristics specified in the General Rules for Preparations (Examples)

Dosage Form	Test Items	
	General Tests (Items to be established in principle)	Items to be investigated such as preparation characteristics stipulated as "appropriate XX"
Tablets, Capsules	· Uniformity of dosage units · Dissolution (Except for effervescent tablets and soluble tablets which are used by dissolving the active ingredient. Stipulate the disintegration when the dissolution is difficult to establish.)	· Disintegration (Orally Disintegrating Tablets)
Granules, Powders	· Uniformity of dosage units (Stipulate for single-dose packages) · Dissolution (Except for the preparations administered after dissolving. Stipulate the disintegration when the dissolution is difficult to establish. However, do not establish disintegration for the preparations not more than 10% of which remain on a No. 30 sieve.)	
Liquids and Solutions for Oral Administration	· Uniformity of dosage units (Stipulate for single-dose packages) · Dissolution (Stipulate for suspensions)	
Syrups	· Uniformity of dosage units (Stipulate for single-dose packages) · Dissolution (Stipulate for suspended products and preparations for syrups. Except for the products to be dissolved only before use. Stipulate the disintegration when the dissolution is difficult to establish. However, do not establish disintegration for the preparations not more than 10% of which remain on a No. 30 sieve.)	
Jellies for Oral Administration	· Uniformity of dosage units · Dissolution (Stipulate appropriate disintegration when the dissolution is difficult to establish.)	· Disintegration
Films for Oral Administration	· Uniformity of dosage units · Dissolution (Except for Orally Disintegrating Films.)	· Disintegration
Tablets for Oro-mucosal Application	· Uniformity of dosage units	· Dissolution or Disintegration
Liquids and Solutions for	· Uniformity of dosage units (Stipulate for single-dose packages)	

Oro-mucosal Application		
Sprays for Oro-mucosal Application		· Uniformity of delivered dose (Metered-dose type preparations)
Semi-solid Preparations for Oro-mucosal Application		· Viscosity
Injections	· Bacterial endotoxins (Except for the preparations used exclusively for intracutaneous, subcutaneous, and intramuscular administration. Stipulate the Pyrogen when the Bacterial endotoxin test is difficult to apply.) · Sterility · Foreign insoluble matter (Except for Implants/Pellets) · Insoluble particulate matter (Except for Implants/Pellets) · Extractable volume (Except for Implants/Pellets) · Uniformity of dosage units (Stipulate for the preparations to be dissolved or suspended before use, and the Implants/Pellets)	· Release characteristic (Implants/Pellets, Prolonged Release Injections and Liposome Injections) · Particle size (Suspended or emulsified preparations and Liposome Injections)
Dialysis Agents	· Bacterial endotoxins · Sterility (Stipulate for Peritoneal Dialysis Agents) · Extractable volume (Stipulate for Peritoneal Dialysis Agents) · Foreign insoluble matter (Stipulate for Peritoneal Dialysis Agents) · Insoluble particulate matter (Stipulate for Peritoneal Dialysis Agents)	· Uniformity of dosage units (For the preparations to be dissolved before use)
Inhalations	· Delivered dose uniformity (Except for Inhalation Liquids and Solutions) · Aerodynamic particle size (Except for Inhalation Liquid and Solutions)	
Ophthalmic Liquids and Solutions	· Sterility · Foreign insoluble matter · Insoluble particulate matter	· Particle size (Maximum particle size of suspended preparations)
Ophthalmic Ointments	· Sterility · Metal particles	· Particle size (Maximum particle size of solid dispersed in preparations) · Viscosity
Ear Preparations	· Sterility (Stipulate in case where preparations are manufactured aseptically)	
Nasal Preparations		· Uniformity of delivered dose (Metered-dose type preparations)
Suppositories for Rectal Application	· Uniformity of dosage units	· Release characteristic · Melting behavior (Method 2 under Melting Point Determination)
Tablets for Vaginal Use,	· Uniformity of dosage units	· Release characteristic
Suppositories for Vaginal Use	· Uniformity of dosage units	· Release characteristic

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		· Melting behavior (Method 2 under Melting Point Determination)
Solid Dosage Forms for Cutaneous Application	· Uniformity of dosage units (Stipulate for single-dose packages)	
Liquids and Solutions for Cutaneous Application	· Uniformity of dosage units (Stipulate for single-dose packages.)	
Sprays for Cutaneous Application		· Uniformity of delivered dose (Metered-dose type preparations)
Ointments, Creams, Gels		· Viscosity
Patches	· Uniformity of dosage units (Stipulate for Percutaneous absorption type preparations) · Adhesiveness · Release characteristic	
Pills	· Disintegration	

In addition, do not specify the Extractable volume for the Powders for Injections and the Freeze-dried Injections. For the test method provided on the preparation characteristic of "appropriate XXX", it may be stipulated as "Being specified separately …" after the investigation of the content by the expert committee. For the Extracts and Fluidextracts, stipulate the heavy metals in principle.

3.22.1.2 Bacterial endotoxins

Specify the Bacterial endotoxins for a preparation which is required to conform to the Bacterial Endotoxins Test as directed under the General Rules for Preparations. Describe the results of the test for interfering factors for the gel-clot technique, the turbidimetric technique and the chromogenic technique together with the actual measurement values by the three techniques in the attached document.

Specify the bacterial endotoxins limit according to the "Decision of Limit for Bacterial Endotoxins" in the General Information of the Japanese Pharmacopoeia. However, for a biological drug substance manufactured by using *Escherichia coli*, etc. as the starting material or that which is manufactured using human/animal-derived materials and is considered necessary to specify the Bacterial endotoxins, specify the Bacterial endotoxins considering the actual measurement values and the General Information.

3.22.1.3 Uniformity of dosage units

Establish the Content uniformity test or the Mass variation test for a preparation which is required to conform to the Uniformity of Dosage Units Test according to the provision in the General Rules for Preparations. For setting the Content uniformity test or the Mass variation test refer to 6.02 Uniformity of Dosage Units Test.

In the case where the quantity of an active ingredient in one dose unit, such as one tablet or one capsule, is not less than 200 mg and, at the same time, the ratio of the active ingredient in the preparation is not less than 70 w/w%, the Mass variation test can be established. Moreover, in the case where the quantity of an active ingredient in one dose unit, such as one tablet or one capsule, at the same time, is not less than 25 mg and the ratio of the active ingredient in the preparation is not less than 25 w/w%, describe "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." and establish the Content uniformity test as "the following method".

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Even in the case where the Mass variation test is established, describe the actual measurement values of the Content uniformity test including individual assay values, mean contents and standard deviations on 3 lots, and acceptance value in the attached document.

3.22.1.4 Dissolution

For a preparation which is required to conform to the Dissolution test or the Disintegration test according to the provision in the General Rules for Preparations, establish the dissolution or the disintegration. For the establishment of the specification for the dissolution, employ the paddle method and 50 rpm as a basic approach, and select pH 6.8 or water as the dissolution medium, if possible, by judging from the required dissolution profiles in standard 4 aqueous solutions. The volume of a test solution is generally 900 mL, and other volumes may be used if the volume is specified in the marketing authorization dossier. In the case of poorly soluble drugs that do not dissolve enough, a surfactant is used and polysorbate 80 is selected as the first choice, and the concentration of the surfactant to be added should be as low as possible. Other surfactants such as sodium lauryl sulfate can be added as necessary. In cases where sedimentation of disintegrated material onto the bottom of the dissolution vessel occurs and sufficient dissolution is not achieved with the paddle method, the basket method at 100 rpm can be employed instead. Set the specification values to the 15% lower level than the mean dissolution rate at the time point when the mean dissolution rate reaches the plateau. It can be considered that the dissolution has reached a plateau when the change in the dissolution rate up to the next time point is approximately not more than 5%. For the drugs having a narrow therapeutic range, stipulate both the upper limit value and the lower limit value at 2 or more time points as necessary. Do not stipulate the acceptance value by the *Q* value except where the *Q* value is specified in the marketing authorization dossier.

In the case of an extended-release preparation, when there is a different formulation design for lasting time of effect, the specification can be established as a separate monograph.

For the powders such as water-soluble vitamins having mild therapeutic effects, the high water solubility and the immediate dissolution profile of 85% or more at 15 minutes, the establishment of the specification for the dissolution is not required. For the preparations among the Preparations for Syrups which are limited to use after dissolving, there is no requirement to establish the dissolution specification.

3.22.2 Other tests for preparations

The alcohol number is the item whose establishment should be considered for Elixirs, Spirits, Tinctures and Fluidextracts. In addition, if there is any other test presumably desirable to be stipulated, such as a test for specific function of a preparation establish the test.

3.22.3 Description order of tests for preparations

Describe the tests for preparations in the order of Bacterial endotoxins (Pyrogen), Metal particles, Extractable volume, Heavy metals, Uniformity of dosage units, Microbial limit, Foreign insoluble matter, Insoluble particulate matter, Disintegration, Sterility, Dissolution, and other tests for preparations.

3.22.4 Description of test for preparations

Describe each test item of the tests for preparations as follows.

Bacterial endotoxins

Describe the Bacterial endotoxins limit as follows.

[Example] 1) Case where the maximum dose is prescribed by volume (mL)

Bacterial endotoxins <*4.01*> Less than *X* EU/mL.

2) Case where the maximum dose is prescribed by mass (mg)

Bacterial endotoxins <*4.01*> Less than *X* EU/mg.

3) Case where the maximum dose is prescribed by equivalent (mEq)

Bacterial endotoxins <*4.01*> Less than *X* EU/mEq.

4) Case where the maximum dose is prescribed by potency

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Bacterial endotoxins <*4.01*> Piperacillin Hydrate Less than 0.07 EU/mg (potency).

5) Case where the provision is necessary only for the limited administration route (e.g. intraspinal administration)

Bacterial endotoxins <*4.01*> Less than *X* EU/mg. Apply for the preparations intended for intraspinal administration.

Metal particles

When performing the test as directed under the Test for Metal Particles in Ophthalmic Ointments, describe as follows:

[Example] Metal particles <*6.01*> It meets the requirement.

Extractable volume

When performing the test for injections as directed under the Test for Extractable Volume of Parenteral Preparations, describe as follows:

[Example] Extractable volume <*6.05*> It meets the requirement.

Uniformity of dosage units

When performing the test as directed under the Uniformity of Dosage Units, describe as follows:

[Example] 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 XXX add *M* mL of YYY, and shake thoroughly until the tablet is completely disintegrated. Add *N* mL of AAA, shake vigorously for *T* minutes, add ZZZ to make exactly *P* mL, and filter. Discard the first *Q* mL of the filtrate, pipet *V* mL of the subsequent filtrate, add ZZZ to make exactly *V'* mL so that each mL contains about *TT* µg of JJJ (molecular formula), and use this solution as the sample solution. (Then, proceed as directed in the Assay.)

[Example] Uniformity of dosage units <*6.02*> Perform the test according to the following method: XXX in single-dose packages meet the requirement of the Content uniformity test.

To the total content of 1 package of XXX add *MM* mL of AAA, ..., and use this solution as the sample solution. (Preparations in single-dose packages)

[Example] Uniformity of dosage units <*6.02*> It meets the requirement of the Mass variation test.

[Example] 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 XXX add *X* mL of XX, and shake thoroughly until the tablet is completely disintegrated. Add *Y* mL of XX, shake vigorously for *T* minutes, add YY to make exactly *Z* mL, and filter. Discard the first *W* mL of the filtrate, pipet *V* mL of the subsequent filtrate, add YY to make exactly *V'* mL so that each mL contains about *U* µg of YYY (molecular formula), and use this solution as the sample solution. (Then, proceed as directed in the Assay.)

However, *T* value can be established in unavoidable cases. In the case where *T* values are established, describe as follows, respectively.

[Example] Uniformity of dosage units <*6.02*> Perform the test according to the following method: it meets the requirement of the Content uniformity test (*T*: ZZ).

[Example] Uniformity of dosage units <*6.02*> It meets the requirement of the Mass variation test (*T*: ZZ).

Microbial limit

When performing the test as directed under the Microbial Limit Test, describe as follows:

[Example] Microbial Limit <*4.05*> The acceptance criteria of TAMC and TYMC are 10^2 CFU/mL and 10^1 CFU/mL, respectively. *Escherichia coli* is not observed.

Note —TAMC : Total Aerobic Microbial Count
TYMC : Total Combined Yeasts/Moulds Count

Foreign insoluble matter

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When performing the test for the injections as directed under the Foreign Insoluble Matter Test for Injections, describe as follows:

[Example] Foreign insoluble matter <*6.06*> Perform the test according to Method 1: it meets the requirement.

When the test is performed with the aqueous solution of ophthalmic solutions as directed under the Foreign Insoluble Matter Test for Ophthalmic Liquids and Solutions, describe as follows:

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

When the test is performed with the suspensions as directed under the Foreign Insoluble Matter Test for Injections or for Ophthalmic Liquids and Solutions, describe as follows.

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

[Example] Foreign insoluble matter <*6.11*> Easily detectable foreign matters are not observed.

Insoluble particulate matter

When performing the test for the injections as directed under the Insoluble Particulate Matter Test for Injections, describe as follows:

[Example] Insoluble particulate matter <*6.07*> It meets the requirement.

[Example] Insoluble particulate matter <*6.07*> Perform the test according to Method 2: it meets the requirement.

When the test is performed with the ophthalmic solutions as directed under the Insoluble Particulate Matter Test for Ophthalmic Solutions, describe as follows:

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

Disintegration

When performing the test as directed under the Disintegration Test, describe as follows:

[Example] Disintegration <*6.09*> It meets the requirement.

[Example] Disintegration <*6.09*> Perform the test using the disk: it meets the requirement.

Sterility

When performing the test as directed under the Sterility Test, describe as follows:

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

Dissolution

When performing the test as directed under the Dissolution Test, describe operating conditions, the specification value, and a test procedure, as a rule.

For the dissolution medium, stipulate the test solution name or details of the composition of the medium in the text about the operating conditions, and describe it using the term “dissolution medium” in the test procedure. Use the term “water” when the dissolution medium is water instead of “dissolution medium”.

Specify the sampling time of the medium in the text about the specification value and describe “specified minute” in the text about the test procedure.

When performing the test as directed under the Dissolution Test, describe as follows:

[Example] Dissolution <*6.10*> When the test is performed at *RR* revolutions per minute according to the Paddle method, using *VV* mL of SSS as the dissolution medium, the dissolution rate in *TT* minutes of XXX is not less than *YY*%.

Start the test with 1 tablet (capsule) of XXX, withdraw not less than *VV* mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding *DD* µm. Discard the first *WW* mL or more of the filtrate, and use the subsequent filtrate as the sample solution. Separately, ..., and use this solution as the standard solution. Determine ..... of the sample solution and standard solution ....

[Example] Dissolution <*6.10*> When the test is performed according to the Flow-through cell method, a large cell (or a small cell), a pump with (or without) pulsation at the flow rate of *BB* mL per minute and the open method (or

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the closed method where the volume of the sample solution is *X* mL), using AAA as the dissolution medium, the dissolution rate in *Y* minutes of XXX is not less than *CC*%.

In the cases where operating conditions and specification values are different according to the product strength or where *Q* value is established as the acceptance value, describe the specification values as follows:

[Example] Dissolution <*6.10*> When the test is performed at *RR* revolutions per minute according to the AAA method, using *VV* mL of SSS as the dissolution medium, the dissolution rate in *TT* minutes of *MM* mg tablet is not less than *YY*%, and that in *UU* minutes of *NN* mg tablet is not less than *ZZ*%.

[Example] Dissolution <*6.10*> When the test is performed at *RR* revolutions per minute according to the Paddle method, using *VV* mL of SSS as the dissolution medium, the *Q* value in *TT* minutes of XXX is *YY*%.

In the cases where the amount of sample for testing varies according to the labeled potency in such cases as granules and powders, start the text of the test procedure as follows.

[Example] Weigh accurately an amount of XXX, equivalent to about *MM* mg of YYY (molecular formulae), and start the test. Withdraw .... at the specified minute ....

Describe as follows when a sinker is used. Specify the shape of a sinker if it is not stipulated in the General Tests.

[Example] Dissolution <*6.10*> When the test is performed at *RR* revolutions per minute according to the Paddle method using a sinker, using *VV* mL of *AA* fluid for dissolution test as the dissolution medium, the dissolution rate in *TT* minutes of XXX is not less than *YY*%.

In the case where further dilution is required in the preparation of the sample solution, describe the preparation procedure of the sample solution as follows.

[Example] Start the test with 1 tablet (capsule) of XXX, withdraw not less than *X* mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding *DD* µm. Discard the first *Y* mL or more of the filtrate, and pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that each mL contains about *MM* µg of YYY (molecular formulae), and use this solution as the sample solution.

Describe the formula as follows.

[Example] Antibiotics

Dissolution rate (%) with respect to the labeled amount of cefteram ($C_{16}H_{17}N_9O_5S_2$)

$= M_S \times A_T/A_S \times V'/V \times 1/C \times 90$

M_S: Amount [mg (potency)] of Cefteram Pivoxil Mesitylene Sulfonate RS taken

C: Labeled amount [mg (potency)] of cefteram ($C_{16}H_{17}N_9O_5S_2$) in 1 tablet

Delayed-release Dosage Forms:

[Example] Dissolution <*6.10*> When the test is performed at *X* revolutions per minute according to the Paddle method, using 900 mL each of 1st fluid for dissolution test and 2nd fluid for dissolution test as the dissolution medium, the dissolution rate in *T* minutes of XXX using 1st fluid is not more than *XX*%, and that in *U* minutes of XXX using 2nd fluid is not less than *YY*%.

Start the test with 1 tablet (capsule) of XXX, withdraw not less than *Y* mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding *Z* µm. Discard not less than *W* mL of the first filtrate, and ....

Extended-release Dosage Forms:

[Example] Dissolution <*6.10*> When the test is performed at *R* revolutions per minute according to the Paddle method, using *A* mL of XX as the dissolution medium, the dissolution rates of XXX in T_1 hours, in T_2 hours and in T_3 hours are $D_A - D_B$%, $D_D - D_E$% and not less than D_F%, respectively, and follows the Interpretation 1.

Melting behavior of suppositories When performing the test according to Method 2 under Melting Point Determination <*2.60*>, describe as follows.

[Example] Melting behavior of suppositories Perform the test according to Method 2 under Melting Point Determination <*2.60*>: the melting range is between *XX*°C and *YY*°C.

3.23 Other tests

3.23.1 Setting of other tests

Items that are directly related to quality evaluation, efficacy and safety of a drug and are not covered otherwise can be established if necessary. These tests include Digestion test, Acid-consuming capacity test, Thymol, Precipitation test, Molecular weight test, Distribution of molecular weight, Nitrogen content, Protein content, Isomer ratio, biochemical performance, and biological performance, etc.

3.23.2 Description order of other tests

The test items are described in the order of the Japanese syllabary.

3.24 Assay or the content of ingredients

3.24.1 Assay

Assay is a method to determine content, potency, etc. of an ingredient by physical, chemical or biological procedures.

3.24.2 Setting of Assay

Set the assay emphasizing accuracy, precision and reproducibility, and considering rapidity. It is desirable to establish the relative testing methods such as highly specific chromatography and ultraviolet-visible spectrophotometry.

If the limit of a contaminant is controlled by appropriate purity test methods, the test method to determine the absolute amount with good reproducibility can be established, even if the method specificity is low.

For example, when the absolute quantitative analysis such as the titration method is selected, in order to cover the low specificity of such method, it is desirable to compensate for the specificity with each other by using a highly specific method for the purity test and so on.

3.24.2.1 Assay of a preparation

Establish the highly specific test method free from the influence of the other ingredients for the assay of a preparation.

In principle, use 20 units or more of the sample.

For setting the calculation equation, set an equation calculating the amount of the substance to be assayed in the taken amount of the sample when the powdered sample is used, or in the one unit sample (1 tablet or 1 capsule) when the whole of the sample is dissolved without pulverizing.

When the content of a biological preparation is calculated based on the results by the assay method of the lyophilized form, examine the test procedure and the equation in order to clarify how to determine the content per single unit (vial and so on). In addition, specify physical quantity (protein content) when the dosage is specified in physical quantity, or potency (biological activity) when specified in a unit (including cases when determining the content by a physicochemical method and expressing the potency by using a conversion factor between the content and the potency) as the assay of preparations.

3.24.3 Assay of protein drug

In the case where the content for a protein drug is specified by the potency per protein, generally specify the assay as (1) Protein content and (2) Specific activity. Express the potency in unit, not in international or other unit. Refer to “Total Protein Assay” of the General Information for protein assay.

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3.24.4 Description about partial sampling of the test solution or back titration

In assay, if a portion of the sample solution is taken or the standard solution for volumetric analysis is added beforehand for the back titration, write the word “exactly”.

[Example] “Pipet 10 mL of the sample solution, add exactly 10 mL of 0.01 mol/L silver nitrate VS ....”

3.24.5 Description of blank determination in the titration

Blank determination in the titration method is described as follows:

Direct titration	“Perform a blank determination in the same manner, and make any necessary correction.”
Back titration	“Perform a blank determination in the same manner.”

3.24.6 Description of equivalent amount in titration

In titration, express the equivalent amount in ‘mg’, with four digits.

Calculate the equivalent amount from molecular mass or formula mass defined in accordance with 3.7.3.

3.24.7 Description of endpoint in titration

Describe merely “titrate” if the end point in titration is the same as that in standardization of the Standard Solution for Volumetric Analysis.

If the end point in titration is different from that in standardization of the Standard Solution for Volumetric Analysis, for example, describe “the endpoint is reached when the color of the solution changes from purple through blue-green to yellow-green” for the indicator method using the crystal violet TS.

3.24.8 Mixing ratio of acetic anhydride and acetic acid (100) used for titration

The mixture of acetic anhydride and acetic acid (100) for titration should be basically 7:3 in the mixing ratio. If acetic acid for non-aqueous titration is used, check in advance whether acetic acid (100) can be used or not.

3.25 Containers and Storage

Specify the container generally. Specify also the storage condition when any special matter is noted for stability.

The revision of paragraph 5 of General Notices indicates that containers under “Containers and storage” for preparations except preparations containing a crude drug as a main active ingredient are not regarded as the acceptance criteria, however describe containers as before for providing information.

[Example] Containers and storage

Containers — Hermetic containers, and colored containers may be used.
Plastic containers for aqueous injections may be used.

Storage — Light-resistant.

(*Note: Describe Storage first in the Japanese version and Containers first in the English version.*)

3.26 Shelf life

Shelf-life is not established in principle, but it may be established for the products whose shelf-life is less than 3 years.

[Example] Shelf life 24 months after preparation.

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3.27 Others

3.27.1 Principle of reference

Do not cross-refer between the Monographs in principle, except for applying a description of a drug substance to a preparation that directly uses the drug substance or applying within the same monograph. Do not cross-refer the referred description (double-deck referring).

4. Description in using Chromatography, etc.

In the case using Liquid Chromatography *<2.01>*, Gas Chromatography *<2.02>*, etc., the description of their operating conditions etc. follows the below.

4.1 Items

Description should be divided into two items, “Operating conditions” and “System suitability”.

Describe the setting conditions, etc. of liquid chromatography, gas chromatography, etc. in “Operating conditions”.

In “System suitability”, describe the requirements and their acceptance criteria to be satisfied by the analytical system used for the test.

4.2 Items and example for operating conditions

Describe the following items in “Operating conditions”. Because the inside diameter, length, etc. of column can be partly changed within the range conforming to the system suitability requirement as mentioned in Liquid Chromatography *<2.01>* and Gas Chromatography *<2.02>*, describe the numerical values as a reference at performing the tests and enter the numerical values obtained from the system used for preparation of rationale for establishing the test procedure.

Describe the name (model number) of a column in the field of column information in Form 4. The described column information is disclosed when calling for public comment on the draft.

4.2.1 Example for describing Liquid Chromatography

1) Detector

[Example 1] Detector: An ultraviolet absorption photometer (wavelength: 226 nm).
[Example 2] Detector: A visible absorption photometer (wavelength: 440 and 570 nm).
[Example 3] Detector: A fluorophotometer (excitation wavelength: 281 nm, fluorescence wavelength: 305 nm).
[Example 4] Detector: A photodiode array detector (wavelength: 270 nm; spectrum range of measurement: 220 – 370 nm).

2) Column: Describe the inside diameter and length of the column, the material of chromatographic column, and the particle size and kinds of the packing material used for analysis.

[Example 1] Column: A stainless steel column 8 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).
[Example 2] Column: A resin column 4.6 mm in inside diameter and 50 cm in length, packed with gel type strongly acidic ion-exchange resin for liquid chromatography (degree of cross-linkage: 6%) (11 μm in particle diameter).
[Example 3] Column: A column 4.6 mm in inside diameter and 10 cm in length, composed of octadecylsilanized monolithic silica for liquid chromatography, having a bimodal pore structure with 2 μm macropore and 13 nm mesopore, coated with polyether ether ketone.

3) Column temperature

[Example] Column temperature: A constant temperature of about 40°C.

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4) Reaction coil

[Example] Reaction coil: A polytetrafluoroethylene tube 0.5 mm in inside diameter and 20 m in length.

5) Cooling coil

[Example] Cooling coil: A polytetrafluoroethylene tube 0.3 mm in inside diameter and 2 m in length.

6) Mobile phase: Express the mixture according to 2.7.4. In case using buffer solutions and test solutions not listed in "Reagents, Test Solutions", describe their preparation methods in this term in principle. In the case of using multiple mobile phases as in gradient elution, attach alphabet (A, B, C ･･･).

[Example 1] Mobile phase: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (3 : 2).

[Example 2] Mobile phase: Dissolve 8.70 g of sodium 1-pentanesulfonate and 8.52 g of anhydrous sodium sulfate in 980 mL of water, adjust to pH 4.0 with acetic acid (100), and add water to make 1000 mL. To 230 mL of this solution add 20 mL of methanol.

[Example 3] Mobile phase A: Dissolve 15.6 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water.
Mobile phase B: A mixture of water and acetonitrile (1 : 1).

7) Flowing of mobile phase: Describe the gradient program in tabulated form. Do not describe the re-equilibration time generally.

[Example] 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 – 5	70	30
5 – 35	70 → 40	30 → 60
35 – 65	40	60

8) Reaction temperature: Describe the reaction temperature in an actual analysis as same as the column temperature.

[Example] Reaction temperature: A constant temperature of about 100°C.

9) Cooling temperature: Describe the cooling temperature in an actual analysis as same as the column temperature.

[Example] Cooling temperature: A constant temperature of about 15°C.

10) Flow rate: Describe the flow rate as the retention time of the analyte or the flow rate of the mobile phase at getting the data to justify the establishment of the test procedure. In the case of writing both retention time and flow rate, the retention time is provided for reference.

Designate this term as "Flow rate of the mobile phase" when the reaction reagent is also used for post-labeling derivatization, etc.

Describe the set flow rate in the gradient elution in principle.

[Example 1] Flow rate: Adjust so that the retention time of XXX is about *T* minutes.

[Example 2] Flow rate: 1.0 mL per minute.

[Example 3] Flow rate: 1.0 mL per minute(the retention time of XXX is about *T* minutes).

11) Flow rate of the reaction reagent: Describe the flow rate at getting the data to justify the establishment of the test procedure. When it is the same as the flow rate of mobile phase, description "the same as the flow rate of the mobile phase" is acceptable.

[Example] Flow rate of the reaction reagent: 1.0 mL per minute.

12) Time span of measurement: Describe as the multiple of the retention time of the analyte. For the gradient elution, describe the time.

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[Example 1] Time span of measurement: About *X* times as long as the retention time of XXX, beginning after the solvent peak.
[Example 2] Time span of measurement: For 40 minutes after injection of the sample solution.
[Example 3] Time span of measurement: For *T* minutes after injection, beginning after the solvent peak.

4.2.2 Example for describing Gas Chromatography

1) Detector
[Example 1] Detector: A hydrogen flame-ionization detector.
[Example 2] Detector: A thermal conductivity detector.

2) Column: Describe the inside diameter and length of the column, the material of the chromatographic tube, the name and particle size of packing material, the name of stationary phase liquid, and the thickness of stationary phase, etc., used for analysis.
[Example 1] Column: A glass column 3 mm in inside diameter and 1.5 m in length, packed with porous ethylvinylbenzene-divinylbenzene copolymer for gas chromatography (average pore diameter: 0.0075 µm, 500 – 600 m^2/g) (150 to 180 µm in particle diameter).
[Example 2] Column: A glass column 3 mm in inside diameter and 1.5 m in length, packed with 180 to 250 µm siliceous earth for gas chromatography coated in 1 to 3% with 50% phenylmethyl silicone polymer for gas chromatography.
[Example 3] Column: A fused silica column 0.53 mm in inside diameter and 30 m in length, coated with polyethylene glycol 20 M for gas chromatography in 0.25 µm thickness. Use a guard column if necessary.
[Example 4] Column: A fused silica tube 0.25 mm in inside diameter and 30 m in length, coated with 5% diphenyl-95% dimethylpolysiloxane for gas chromatography in 0.25 µm thickness.

3) Column temperature
[Example 1] Column temperature: A constant temperature of about 210°C.
[Example 2] Column temperature: Maintain the temperature at 40°C for 20 minutes, then raise to 240°C at a rate of 10°C per minute, and maintain at 240°C for 20 minutes.
[Example 3] Column temperature: Inject at a constant temperature of about 100°C, then raise the temperature to 220°C at a rate of 7.5°C per minute, and maintain at a constant temperature of about 220°C.

4) Injection port temperature: Describe if the temperature control is important.
[Example] Injection port temperature: 140°C.

5) Detector temperature: Describe if the temperature control is important.
[Example] Detector temperature: 250°C.

6) Carrier gas
[Example] Carrier gas: Helium.

7) Flow rate: Describe the linear velocity in principle. If it is difficult to obtain the linear velocity, the retention time of the analyte can be described.
[Example 1] Flow rate: 35 cm per second.
[Example 2] Flow rate: Adjust so that the retention time of XXX is about *TT* minutes.

8) Split ratio: Express the split ratio assuming the flow rate of the carrier gas in the column is 1 in principle.
[Example 1] Splitless.
[Example 2] Split ratio: 1:5.

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9) Time span of measurement: Describe as the multiple of the retention time of the analyte.
[Example] Time span of measurement: About *X* times as long as the retention time of XXX, beginning after the air peak.

10) Operating conditions of head-space apparatus
Parameter names and injection conditions are described appropriately for each instrument manufacturer. The amount of sample to be injected should be set appropriately to meet the criteria of the test method, considering the injection volume recommended by the instrument manufacturer.
[Example] Perform the test as directed in the head-space method under Gas Chromatography <*2.02*> according to the following conditions.
Head-space injection conditions
Equilibration temperature in vial: 80°C.
Equilibration time in vial: 60 minutes.
Transfer-line temperature: 85°C.
Syringe temperature: 80 – 90°C.
Carrier gas: Nitrogen or helium at an appropriate pressure.
Pressurization time: 60 seconds or more.
Injection volume: 1 mL.

4.3 System suitability

4.3.1 Purpose

"System suitability" is intended to confirm that the analysis system used for the test of a drug is run with the appropriate performance that is suitable for the test of the drug concerned for each series of quality tests. In other words, confirm that specificity for the test component is ensured, and the extent of variation (precision) in the response of the test component is at a level that meets the purpose of the test when the standard solution or system suitability test solution is repeatedly injected. In addition, in the purity test, confirm that the peaks of the target related substances, etc. are reliably detected at the concentration of the specification limit levels. The test procedure and acceptance requirements of the system suitability should be specified in the test method which is set in the quality specification of the drug. Do not accept the results of the quality test using the analytical system when it does not satisfy the specified requirements.

Because the system suitability has characteristics as the routine test performed for each series of analyses, it is preferable to establish the method which can confirm without consuming a lot of time and work. As 4.3.2 was described using a chemical drug as an example, specify the items necessary to evaluate whether the appropriate conditions for performing quality test are maintained or not, according to the characteristics of the product and the purpose of the test.

4.3.2 Items of system suitability

Unless otherwise specified, specify "System performance" and "System repeatability". In the Purity, the "Test for required detectability" may be required in addition to them. When appropriate, the system suitability items specified in Chromatography<*2.00*> can be used to evaluate the system suitability, and the items can be combined. For example, "Test for required detectability" described in Liquid Chromatography <*2.01*> can be evaluated by the provision described in Chromatography <*2.00*>, and "system performance" can be evaluated by the provision described in Liquid Chromatography <*2.01*>. However, within each item of "Test for required detectability", "System suitability", and "System repeatability" described in Liquid Chromatography <*2.01*>, the contents specified in Chromatography <*2.00*> can not be combined with the contents specified in <*2.01*>.

4.3.2.1 Test for required detectability

"Test for required detectability" verifies that the chromatographic system to be used has the performance necessary for attaining the purpose of the test by confirming that the peaks of the target related substances, etc. in the Purity are detected definitely at the concentration of the acceptance limit level.

In quantitative tests such as obtaining total related substances, etc., specify the response range when the solution at the concentration of the acceptance limit level is injected, and demonstrate the linearity of the response around the acceptance limit. Specify the allowable response range by the span of ±30% of the theoretical value in principle such as "7–13%". If the value is a decimal fraction, round it to the inside of ± 30%. Alternatively, specify the SN ratio when a solution is injected at the lowest concentration level (in the case of chemical drugs, this corresponds to the reporting threshold generally) that should be controlled taking into account the nature of an analyte. The SN ratio must be not less than 10.

The term of "Test for required detectability" may not be specified in the case of performing the test comparing the standard solution whose concentration is at the acceptance limit such as the limit test and in the case where the precision at the level of the acceptance limit can be confirmed by the "System repeatability", etc.

4.3.2.2 System performance

"System performance" verifies that the chromatographic system to be used has performance necessary for attaining the purpose of the test by confirming that the specificity of the test component is ensured.

In the Assay, prescribe it by the resolution between the analyte and the target substance to be separated (neighboring peak is preferable, and in case where the internal standard method is used, the internal standard is preferable) in principle. Additionally specify their order of elution as needed. In the Purity specify the resolution and the order of elution between the analyte and the target substance to be separated (neighboring peak is basically preferable) in principle. If necessary, specify the symmetry factor in addition. The specification by the number of theoretical plates and the symmetry factor of the peak of the analyte is, however, acceptable if no reference standard for system suitability or no appropriate target substance to be separated is available. In the case of liquid chromatography using the gradient method and temperature-programmed gas chromatography, it is not possible to specify the number of theoretical plates, so it is necessary to specify the resolution by using a target substance to be separated. For the resolution, specify it by two significant figures when the resolution is less than 3, and specify it by one significant figure when the resolution is not less than 3. When the leading of the peak is observed, specify the symmetry factor of the peak in range.

In "System performance" the use of a peak-valley ratio instead of resolution is judged individually.

For the establishment without using a reference standard for system suitability, it is desirable to establish system performance using the standard solution, not preparing a solution by weighing the Reference Standard newly for the term of "System performance". When the resolution between the analyte and the degradation product is specified by decomposing the drug substance, it is necessary that the amount of the degradation product is sufficient, and the degradation conditions are shown as in detail as possible. The solution for system suitability test may also be prepared by adding the JP reagent, etc., but even in such a case do not use a special reagent commercially unavailable, such as the reference material of related substance which may have safety concern, etc. in principle.

4.3.2.3 System repeatability

The "System repeatability" verifies that the chromatographic system to be used has performance necessary for attaining the purpose of the test by confirming that the degree of variation (precision) of response of the analyte is at the level of suitable for the purpose of the test when the standard solution or the solution for system suitability test is injected repeatedly.

Specify it generally by the relative standard deviation (RSD) of responses of the analyte obtained by repeated injections of the standard solution or the solution for system suitability test. When the system suitability in the Assay is applied to the Purity, the system repeatability in the Assay should not be applied to the Purity. Establish it using the standard solution in the Purity test or the solution for system suitability test in principle. The system repeatability may be confirmed not only by repeating injections of the standard solution before starting the injections of the sample solution but also by dividing them into before and after the injections of the sample solution or by inserting them between the injections of the sample solution.

The number of replicate injections is 6 in principle, but when a cycle time of analysis is long, such as a gradient elution or an existence of a slow eluting component in the sample etc., the number of replicate injections could be reduced by tightening the allowance limit of variation to be attained in order to ensure the system repeatability comparable with that with six injections. However, in the area-percentage method, if the influence of a matrix is assessed, and an appropriate test for required detectability such as using a solution with the lowest concentration level that should be controlled is established taking into account the properties of an analyte, the provision for system reproducibility may not be necessary.

Specify the allowance limit of variation at an appropriate level based on the validation data under for the study of application of the test procedure.

4.3.3 Items of system suitability applying Chromatography <*2.00*>

The number of theoretical plates, retention factor (mass distribution ratio), system repeatability, SN ratio, symmetry factor, and resolution/peak-valley ratio may be used to evaluate the performance of a chromatography system. However, in the case of the gradient method, the number of theoretical plates cannot be specified. When applying Chromatography <*2.00*>, use the terms such as “peak symmetry”, “resolution” employed in Chromatography <*2.00*> as described in Examples 3, 4, 12 and 13 of 4.3.4.1 and the name of item “System performance” should not be used. When the conditions outlined in the "System Suitability" section of Chromatography <*2.00*> cannot be applied, such as in cases where the target content of the active ingredient is not 100%, the provisions in <*2.01*> can be used.

In order to confirm that specificity for the test component is ensured in the Purity, etc. and the Assay, set "Resolution" as well as " Peak symmetry." Unless otherwise specified, the symmetry factor of a peak (tailing factor) used for purity tests and assay is 0.8 to 1.8 in principle. In addition, "Resolution" is specified with two significant digits if it is less than 3, and with one significant digit if it is 3 or more. In addition, if it is difficult to specify "Resolution" (for example, if "Resolution" is less than 1.5), "peak-valley ratio" can be set.

In "System repeatability" the limit value of the maximum permitted relative standard deviation (%RSD_{max}) , which is calculated by replicate injections (n = 3 to 6) of the standard solution, is specified in the determination of active ingredients or excipients, when the target value of those pure substances is 100%. In other words, the maximum permitted relative standard deviation of the peak response does not exceed the appropriate value given in Table 2.00-1 in Chromatography <*2.00*>.

In the Purity, etc., set ”"System sensitivity” to confirm that the peaks of target impurities are reliably detected at the concentrations of the specification limit levels. The SN ratio is used to define the system sensitivity. The limit of quantification (corresponding to an SN ratio of 10) is below the reporting threshold. The reporting threshold should also be described in the test method.

4.3.4 Examples for the description for system suitability

Examples for the description for system suitability of liquid chromatography are shown below.

4.3.4.1 General examples

[Example 1] Assay

System performance: When the procedure is run with V µL of the standard solution under the above operating conditions, XXX and the internal standard are eluted in this order with the resolution between these peaks being not less than *M.M*.

System repeatability: When the test is repeated 6 times with V µL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of XXX to that of the internal standard is not more than 1.0%.

[Example 2] Assay

System performance: Dissolve X g of XXX and Y g of YYY in V mL of MMM. When the procedure is run with W µL of this solution under the above operating conditions, XXX and YYY are eluted in this order with the resolution between these peaks being not less than *XX*.

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

[Example 3] Assay (when applying Chromatography <*2.00*> and the target value of an active substance or an excipient is not 100%)

Peak symmetry: When the procedure is run with V mL of a solution of XXX under the above operating conditions, the symmetry factor of the peak of YYY is 0.8 to 1.8.

Resolution: When the procedure is run with V mL of the standard solution under the above operating conditions, the resolution between XX and the internal standard is not less than *MM*.

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System repeatability: When the test is repeated 6 times with *V* μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of XXX to that of the internal standard is not more than 1.0%.

[Example 4] Assay (when applying Chromatography <*2.00*> and the target value of an active substanceor an excipient is 100% [excluding drug products)]

Peak symmetry: When the procedure is run with *V* mL of a solution of XXX solution under the above operating conditions, the symmetry factor of the peak of YYY is 0.8 to 1.8.

Resolution: When the procedure is run with *V* mL of the standard solution under the above operating conditions, the resolution between XX and the internal standard is not less than *MM*.

System repeatability: When the test is repeated 5 times with *V* μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of XXX is not less than *MM* according to Chromatography <*2.00*> Table 2.00-1.

[Example 5] Purity

Test for required detectability: Pipet *V* mL of the standard solution, and add MMM to make exactly *VV* mL. Confirm that the peak area of XXX obtained with *W* μL of this solution is equivalent to *XX* to *YY* % of that with *W* μL of the standard solution.

System performance: Dissolve *X* g of XXX and *Y* g of YYY in *V* mL of MMM. When the procedure is run with *W* μL of this solution under the above operating conditions, XXX and YYY are eluted in this order with the resolution between these peaks being not less than *XX*.

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

[Example 6] Purity

Test for required detectability: To *V* mL of the sample solution add MMM to make *VV* mL, and use this solution as the solution for system suitability test. Pipet *W* mL of the solution for system suitability test, and add NNN to make exactly *WW* mL. Confirm that the peak area of XXX obtained with *U* μL of this solution is equivalent to *XX* to *YY* % of that with *U* μL of the solution for system suitability test.

System performance: When the procedure is run with *U* μL of the solution for system suitability test under the above operating conditions, the number of theoretical plates and symmetry factor of the peak of XXX are not less than *MM* and not more than *NN*, respectively.

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

[Example 7] Purity (when a reference standard for system suitability is the mixture of related substances and contains no drug substance AAA)

Test for required detectability: To exactly *X* mL of the standard solution add XX to make exactly *Y* mL. Confirm that the peak area of XXX obtained with *Z* μL of this solution is equivalent to *XX* to *YY*% of that with *Z* μL of the standard solution.

System performance: Dissolve *X* mg of AAA for System Suitability RS in the mobile phase to make *Y* mL. To this solution add *Z* mL of the standard solution. When the procedure is run with *W* μL of this solution under the above operating conditions, identify the peaks of related substances A, B and C, having the relative retention times of about *TA*, *TB* and *TC* to BBB, respectively. The resolutions between the peaks of related substance A and related substance B, between the peaks of related substance B and CCC, and between the peaks of DDD and related substance C are not less than *XX*, not less than *YY*, and not less than *ZZ*, respectively. (Specify plural resolutions as necessary.)

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

[Example 8] Purity (when a reference standard for system suitability is the mixture of related substances and drug substance AAA)

Test for required detectability: To *X* mL of the sample solution add XX to make *Y* mL, and use this solution as the solution for system suitability test. Pipet *Z* mL of the solution for system suitability test, and add YY to

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make exactly W mL. Confirm that the peak area of AAA obtained with V μL of this solution is equivalent to XX to YY% of that with V μL of the solution for system suitability test.

System performance: Dissolve X mg of AAA for System Suitability RS in XX to make Y mL. When the procedure is run with Z μL of this solution under the above operating conditions, identify the peaks of related substances A, B, C and D, having the relative retention times of about TA, about TB, about TC and about TD to AAA, respectively. The resolutions between the peaks of related substance B and BBB, and between the peaks of CCC and related substance C are not less than XX and not less than YY, respectively. (Specify plural resolutions as necessary)

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

[Example 9] Purity (when a reference standard for system suitability is a related substance)

Test for required detectability: To X mL of the sample solution add XX to make Y mL, and use this solution as the solution for system suitability test. Pipet Z mL of the solution for system suitability test, and add YY to make exactly W mL. Confirm that the peak area of AAA obtained with V μL of this solution is equivalent to A to B% of that with V μL of the solution for system suitability test.

System performance: Dissolve X mg of AAA RS, Y mg of AAA Related Substance B for System Suitability RS and Z mg of AAA Related Substance C for System Suitability RS in XX to make W mL. When the procedure is run with V μL of this solution under the above operating conditions, related substance B, XXX and related substance C are eluted in this order with the resolutions between the peaks of related substance B and XXX, and between the peaks of XXX and related substance C being not less than XX, respectively.

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

[Example 10] Purity (when the reference standard of a related substance is used for a quantitative test)

Test for required detectability: Pipet X mL of the standard solution, and add XX to make exactly Y mL. Confirm that the peak area of XXX obtained with Z μL of this solution is equivalent to XX to YY% of that with Z μL of the standard solution.

System performance: When the procedure is run with X μL of the standard solution under the above operating conditions, the relative retention times to AAA of related substances A and B are TA and TB and the resolutions between the peaks of related substances A and B and between the peaks of related substance B and XXX are not less than XX, and not less than YY, respectively.

System repeatability: To X mL of the standard solution add the mobile phase to make Y mL. When the test is repeated 6 times with X μL of this solution under the above operating conditions, the relative standard deviations of the peak area of related substance A, B and XXX are not more than XX, respectively.

[Example 11] Purity (when in the area percentage method the influence of a matrix has been assessed, and an appropriate test for required detectability such as using a solution with the lowest concentration level to be controlled has been established, taking into account the properties of an analyte)

Test for required detectability: To X mL of the sample solution add XX to make Y mL, and use this solution as the solution for system suitability test. Pipet Z mL of the solution for system suitability test, and add YY to make exactly W mL. When the procedure is run with X μL of this solution under the above operating conditions, the SN ratio of the peak of AAA is not less than 10.

System performance: When the procedure is run with X 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 AAA are not less than XX and not more than YY, respectively.

[Example 12] Purity (when applying Chromatography <*2.00*>)

System sensitivity: To X mL of the sample solution add XX to make Y mL, and use this solution as the solution for system suitability test. Pipet Z mL of the solution for system suitability test, and add YY to make

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exactly W mL. When the procedure is run with X µL of this solution under the above operating conditions, the SN ratio of the peak of AAA is not less than 10.

Peak symmetry: When the procedure is run with X µL of a solution of XXX under the above operating conditions, the symmetry factor of the peak of YYY is 0.8 to 1.8.

Resolution: Dissolve X g of XXX and Y g of YYY in V mL of MMM. When the procedure is run with V µL of this solution under the above conditions, the resolution between the peaks of XX and YY is not less than *M.M*.

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

[Example 13] Purity (when applying Chromatography <*2.00*> and the resolution cannot be set)

System sensitivity: To X mL of the sample solution add XX to make Y mL, and use this solution as the solution for system suitability test. Pipet Z mL of the solution for system suitability test, and add YY to make exactly W mL. When the procedure is run with X µL of this solution under the above operating conditions, the SN ratio of the peak of AAA is not less than 10.

Peak symmetry: When the procedure is run with X µL of a solution of XXX under the above operating conditions, the symmetry factor of the peak of YYY is 0.8 to 1.8.

Peak-valley ratio: When the procedure is run with V µL of the standard solution under the above conditions, the peak-valley ratio of the related substances A and B is not less than *M.M*.

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

4.3.4.2 Other examples of description for "System performance"

1) Stipulating elution order, resolution and symmetry factor

[Example] Dissolve M g of XXX and N g of YYY in V mL of SSS. When the procedure is run with W µL of this solution under the above operating conditions, XXX and YYY are eluted in this order with the resolution between these peaks being not less than *AA* and the symmetry factor of the peak of XXX is not more than *B.B*.

2) Stipulating elution order, resolution, number of theoretical plates and symmetry factor

[Example] Dissolve M g of XXX and N g of YYY in V mL of SSS. When the procedure is run with W µL of this solution under the above operating conditions, XXX and YYY are eluted in this order with the resolution between these peaks being not less than *AA*, and the number of theoretical plates and the symmetry factor of the peak of XXX are not less than *TT* and not more than *BB*, respectively.

3) Stipulating number of theoretical plates and symmetry factor because an appropriate target substance to be separated is not available

[Example] Dissolve M g of XXX in V mL of SSS. When the procedure is run with W µL of this solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of XXX are not less than *TT* and not more than *BB*, respectively.

4) Stipulating elution orders and resolutions of the test component and degradation product by forced degradation of the sample solution

[Example] Heat the sample solution in a water bath at T°C for M minutes, and cool. To V mL of this solution add SSS to make W mL. When the procedure is run with U µL of this solution under the above operating conditions, the resolution between the peak, having the relative retention time to XXX of about T, and the peak of XXX is not less than *AA,* and the symmetry factor of the peak of XXX is not more than *B.B*.

4.3.4.3 Examples of description of system suitability for tests specific to biological products

Among the tests specific to biological products, the examples of system suitability for tests using liquid chromatography and electrophoresis are given below. Depending on the properties of a sample to be analyzed, system performance may specify the resolution between peaks or the number of peaks, or compare with the chromatogram* of Reference Standard. In tests using the

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area percentage method, system repeatability may not be set, however the system repeatability can be confirmed by analyzing a standard solution repeatedly or at the beginning and end of the test to ensure that a similar separation pattern is obtained.
* Chromatogram of Reference Standard: A chromatogram described in the attachment document of a reference standard.

4.3.4.3.1 Identification

4.3.4.3.1.1 Peptide map

When the specification is “compare the chromatograms from standard and sample solutions: both chromatograms show the similar peaks at the corresponding retention time.”, etc.

[Example 1] (In the case using the chromatogram of Reference Standard)

System performance: When the procedure is run with *X* µL of the standard solution under the above operating conditions, the chromatogram shows a similar peak at the similar retention time as the standard chromatogram of the reference standard.

[Example 2] (In the case not using the chromatogram of Reference Standard)

System performance: When the procedure is run with *X* µL of the standard solution under the above operating conditions, the chromatogram shows principal *Y* peaks and the resolution between the peak A and peak B is not less than *Z*.

4.3.4.3.2 Specific physical and/or chemical values

4.3.4.3.2.1 Oligosaccharide profile

When the specification is “the chromatograms obtained from the sample solution and standard solution are similar, and the area percentages of the peaks 1, 2, 3 and 4 are *XX-YY*, *ZZ-WW*, *VV-UU* and *TT-SS*, respectively.”, etc.

[Example 1] (In the case using the chromatogram of Reference Standard)

System performance: When the procedure is run with *X* µL of the standard solution under the above operating conditions, the chromatogram shows a similar peak at the similar retention time as the standard chromatogram of the reference standard.

[Example 2] (In the case not using the chromatogram of Reference Standard)

System performance: When the procedure is run with *X* µL of the standard solution under the above operating conditions, the chromatogram shows the peaks 1, 2, 3 and 4, and the resolution between the peak 2 and the peak 3 is not less than *Z*.

4.3.4.3.2.2 Charge profile (Ion exchange chromatography)

When the specification is “the area percentages of the principal peak and the peak groups in the acidic and basic regions are *XX-YY*%, *ZZ-WW*% and *VV-UU*%.”, etc.

[Example 1] (In the case using the chromatogram of Reference Standard)

System performance: When the procedure is run with *X* µL of the standard solution under the above operating conditions, the chromatogram shows a similar peak at the similar retention time as the standard chromatogram of the reference standard.

[Example 2] (In the case not using the chromatogram of Reference Standard)

System performance: When the procedure is run with *X* µL of the standard solution under the above operating conditions, the resolution between the principal peak and the peak A is not less than *Z*.

4.3.4.3.3 Purity

4.3.4.3.3.1 SDS capillary gel electrophoresis

When the specification is “The ratio of the principal peak is not less than *XX*%, and the ratio of A is not more than *YY*%.”, etc.

[Example]

Test for required detectability: To *X* mL of the standard solution add *Y* mL of a solution of AAA. When the procedure is run with *X* µL of this solution under the above operating conditions, confirm that the area of the principal peak obtained with this solution is *X* - *Y*% of that with the standard solution.

System performance: When the procedure is run with *X* µL of the standard solution under the above operating conditions, the resolution between the principal peak and the peak A is not less than *Z*.

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4.3.4.3.3.2 Fragments SDS-polyacryleamide gel electrophoresis

When the specification is "The ratio of the principal band at the position corresponding the molecular weight of about XXXX is not less than *XX*%, the total ratio of the other bands is not more than *YY*%, and the ratio of each band is not more than *ZZ*%.", etc.

[Example]

Test for required detectability: To *X* mL of the standard solution add *Y* mL of a solution of AAA. When the procedure is run with *X* µL of this solution under the above operating conditions, the principal band appears.

System performance: X bands appear in the lane of the molecular weight marker.

4.4 Other examples of description

4.4.1 Gradient method

[Example]

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 octadecylsilanized silica gel for liquid chromatography (5 µm in particle diameter).

Column temperature: A constant temperature of about *TT*°C.

Mobile phase A: A mixture of water and acetonitrile for liquid chromatography (4:1).

Mobile phase B: A mixture of acetonitrile for liquid chromatography and water (3:2).

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%)
$0 - X$	X	X
$X - X$	$X \rightarrow X$	$X \rightarrow X$
$X - X$	X	X

Flow rate: 1.0 mL per minute.

Time span of measurement: About *X* times as long as the retention time of XXX, beginning after the solvent peak.

: For *T* minutes after injection, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet *X* mL of the standard solution, and add XX to make exactly *W* mL. Confirm that the peak area of XXX obtained with *V* µL of this solution is equivalent to *YY* to *ZZ* % of that with *V* µL of the standard solution.

System performance: Dissolve *X* g of XXX and *Y* g of YYY in *W* mL of MMM. When the procedure is run with *V* µL of this solution under the above operating conditions, XXX and YYY are eluted in this order with the resolution between these peaks being not less than *XX*.

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

4.4.2 Temperature gradient gas chromatography

[Example]

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A fused silica capillary column 0.32 mm (or 0.53 mm) in inside diameter and 30 m in length, coated with polyethylene glycol 20M for gas chromatography in thickness of 0.25 µm. Use a guard column if necessary.

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

Injection port temperature: A constant temperature of about 140°C.

Detector temperature: A constant temperature about 250°C.

Carrier gas: Helium.

Flow rate: 35 cm per second.

Split ratio: 1:5.

System suitability—

System performance: When the procedure is run with *V* µL of the standard solution under the above operating conditions, the resolution of these peaks is not less than 1.5. (Note: in case where there are multiple test compounds)

System repeatability: When the test is repeated 3 times with *V* µL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of AAA is not more than 15%.

5. Examples of Description in Using ICP-Atomic Emission Spectrometry and ICP-Mass Spectrometry

5.1 ICP-Atomic Emission Spectrometry

[Example]

1) Assay Weigh accurately about *X* mg of AAA, add *Y* mL of XX acid, heat to dissolve, cool, and add water to make exactly *Z* mL. Pipet *W* mL of this solution, add *V* mL of XX acid and water to make exactly *U* mL, and use this solution as the sample solution. To *T* mL of XX acid add water to make exactly *S* mL, and use this solution as the blank solution. Pipet *R* mL, *Q* mL, *P* mL and *O* mL of Element # Standard Solution (*XX* ppm), add water to make exactly *N* mL each, and use these solutions as the element # standard solutions (1), (2), (3) and (4), respectively. Perform the test with the sample solution, blank solution, and element # standard solutions (1), (2), (3) and (4) as directed under Inductively Coupled Plasma-Atomic Emission Spectrometry <*2.63*> according to the following conditions, and determine the content of element # using the calibration curve obtained from the emission intensities of the blank solution and the element # standard solutions.

Operating conditions—

Wavelength: Element # *YYY.YYY* nm

System suitability—

System repeatability: When the test is repeated 6 times with the element # standard solution (1) under the above operating conditions, the relative standard deviation of the emission intensity of element # is not more than *XX*%.

2) Purity Element #—Weigh accurately about *X* mg of AAA, add *Y* mL of XX acid, and digest the sample by heating using a microwave digestion equipment. After cooling, wash the vessel several times with water, then, add water to make exactly Z mL, and use this solution as the sample solution. To *W* mL of BBB acid add water to make exactly *V* mL, and use this solution as the blank solution. Pipet *U* mL of Element # Standard Solution (*XX* ppm), add *T* mL of XX acid, and add water to them to make exactly *S* mL, and use this solution as the element # standard stock solution. Pipet *R* mL, *Q* mL, *P* mL and *O* mL of the element # standard stock solution, add *N* mL of XX acid and water to make exactly *M* mL each, and use these solutions as the element # standard solutions (1), (2), (3) and (4), respectively. Perform the test with the sample solution, blank solution, and element # standard solutions (1), (2), (3) and (4) as directed under Inductively Coupled Plasma-Atomic Emission Spectrometry <*2.63*> according to the following conditions, and determine the content of element # using the calibration curve obtained from the emission intensities of the element # standard solutions (1), (2), (3) and (4): it is not more than *YY* ppm.

Operating conditions—

Wavelength: Element # ZZZ.ZZZ nm

System suitability—

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System repeatability: When the test is repeated 6 times with the element # standard solution (1) under the above operating conditions, the relative standard deviation of the emission intensity of element # is not more than *XX*%.

5.2 ICP- Mass Spectrometry

[Example]

1) Assay Element #―Weigh accurately about *X* mg of AAA, add *Y* mL of XX acid and *Z* mL of YY acid, and gradually heat on a hot-plate until no more brown gas evolves and the solution becomes clear and light yellow. After cooling, add exactly *T* mL of the internal standard solution, add water to make *W* mL, and use this solution as the sample solution. To *Y* mL of XX acid add *Z* mL of YY acid and exactly *T* mL of the internal standard solution, add water to make *W* mL, and use this solution as the blank solution. Pipet *R* mL, *Q* mL, *O* mL and *N* mL of Element # Standard Solution (*XX* ppm), add exactly *M* mL of XX acid, *L* mL of YY acid and *K* mL of the internal standard solution to them, then add water to make *J* mL each, and use these solutions as the element # standard solutions (1), (2), (3) and (4), respectively. Perform the test with the sample solution, blank solution, and element # standard solutions (1), (2), (3) and (4) as directed under Inductively Coupled Plasma-Mass Spectrometry <*2.63*> according to the following conditions, and determine the content of element # from the ratios of the ion counts of the blank solution and the element # standard solutions (1), (2), (3) and (4) to those of the internal standard element.

Internal standard solution―Pipet *X* mL of Element $ Standard Solution (*XX* ppm), and add water to make exactly *Y* mL.

Operating conditions―

Measurement *m*/*z*: element # *m*/*z XX*, element $ *m*/*z YY*.

System suitability―

System repeatability: When the test is repeated 6 times with the element # standard solution (1) under the above operating conditions, the relative standard deviation of the ratio of the ion counts of element # to that of the internal standard element is not more than *XX*%.

2) Purity Element #1, #2 and #3―Weigh accurately about *X* mg of AAA, add *Y* mL of XX acid, and digest the sample by heating using a microwave digestion equipment. After cooling, wash the vessel several times with water, add exactly *Z* mL of the internal standard solution, then add water to make *W* mL, and use this solution as the sample solution. To *Y* mL of XX acid add exactly *Z* mL of the internal standard solution, then add water to make exactly *T* mL, and use this solution as the blank solution. Pipet *S* mL each of Element #1 Standard Solution, Element #2 Standard Solution and Element #3 Standard Solution (*XX* ppm), add *R* mL of BBB acid and water to make exactly *Q* mL each, and use these solutions as the element #1 standard stock solution, the element #2 standard stock solution and the element #3 standard stock solution, respectively. Pipet *P* mL, *O* mL, *N* mL and *M* mL of the element #1, #2 and #3 standard stock solutions, add exactly *L* mL of XX acid and exactly *K* mL of the internal standard solution to them, then add water to make *J* mL each, and use these solutions as the standard solutions (1), (2), (3) and (4) for elements #1, #2 and #3, respectively. When there is no mutual interference, these standard solutions can be used as a mixture. Perform the test with the sample solution, blank solution, and standard solutions (1), (2), (3) and (4) for each element as directed under Inductively Coupled Plasma-Mass Spectrometry <*2.63*> according to the following conditions, and determine the contents of elements #1, #2 and #3 from the ratios of the ion counts of the blank solution and the standard solutions (1), (2), (3) and (4) for elements #1, #2 and #3 to that of the internal standard element: it is not more than *YY* ppm, respectively.

Internal standard solution―Pipet *X* μL of Element $ Standard Solution (*XX* ppm), and add water to make exactly *Y* mL.

Operating conditions―

Measurement *m*/*z*: element #1 *m*/*z XX*, element #2 *m*/*z YY*, element #3 *m*/*z* ZZ, element $ *m*/*z WW*.

Using a collision reaction cell introduction gas (Name of gas, if necessary).

System suitability―

System repeatability: When the test is repeated 6 times with each standard solution (1) for elements #1, #2 and #3 under the above operating conditions, the relative standard deviation of the ratio of the ion counts of element # to that of the internal standard element is not more than *XX*%.

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6. Example of Description in Using Quantitative NMR (qNMR)

Since the ratio of atomic nuclei in a compound is proportional to the peak area ratio in nuclear magnetic resonance spectroscopy, NMR measurement can examine the purity of a compound under the condition that ensure quantitative performance. Quantitative NMR using a reference standard for qNMR is described in Nuclear Magnetic Resonance Spectroscopy *<2.21>* and the concrete test procedures are shown in 10. Assay of Marker Compounds for the Assay of Crude Drugs and Extracts of Kampo Formulations Utilizing Nuclear Magnetic Resonance (NMR) Spectroscopy under Crude Drugs Test *<5.01>*. In Quantitative Analytical Technique Utilizing Nuclear Magnetic Resonance (NMR) Spectroscopy and its Application to Reagents in the Japanese Pharmacopoeia in General Information, the background of setting the test method and commentary on the test method etc. are described.

6.1 Quantitative ^{1}H NMR

In the quantitation by ^{1}H NMR, a substance to be measured and a SI traceable reference standard for qNMR with known purity are accurately weighed, respectively, and are dissolved together in a deuterated solvent, and then ^{1}H NMR is measured with the solution. Quantitative values are calculated by the relationship among the signal areas of the substance of interest and the reference standard for qNMR observed in the obtained spectrum, the numbers of proton, the masses and the molecular masses.

[Example] Assay Weigh accurately X mg of AAA and Y mg of BBB reference standard for nuclear magnetic resonance spectroscopy using an ultramicrobalance, dissolve in Z mL of deuterated XX 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 BBB for nuclear magnetic resonance spectroscopy as the reference standard for qNMR. Calculate the resonance intensities, A_1 (equivalent to N_1 hydrogen) and A_2 (equivalent to N_2 hydrogen), of the signals around δ *XX* ppm and δ *YY* ppm based on the signal of the reference standard for qNMR as δ 0 ppm.

Amount (%) of AAA (molecular formula)

$= M_S \times I \times P / (M \times N) \times$ [(molecular mass of AAA) /(molecular mass of the reference standard for nuclear magnetic resonance spectroscopy)]

M: Amount (mg) of AAA taken

M_S: Amount (mg) of BBB reference standard 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 BBB reference standard for nuclear magnetic resonance spectroscopy as *ZZ*

N: Sum of numbers of the hydrogen derived from A_1 and A_2

P: Purity (%) of BBB reference standard 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 wider, 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 or longer.

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 of around δ *XX* ppm is not less than 100.

System performance: When the procedure is run with the sample solution under the above operating conditions, the two signals of around δ *XX* ppm and δ *YY* ppm are not overlapped with any signal of

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obvious foreign substance, and the ratio of the resonance intensities per a proton, $(A_1／N_1)／(A_2／N_2)$, of each signal around δ *XX* ppm and δ *YY* ppm are between 0.99 and 1.01, respectively.

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

Use a clean NMR tube with high quality (example: Wilmad No.535, FUJIFILM Wako Pure Chemical Corporation SHG-type, SHIGEMI PS-1, etc.) and a deuterated solvent with not less than 99.9% deuteration rate.

The certified reference materials (CRM) accredited by the Accreditation System of National Institute of Technology and Evaluation (ASNITE) of the Accreditation Center for National Institute of Technology and Evaluation (IA Japan) are supplied as reference standards to be used for the SI traceable metrological determination of 1,4-BTMSB-d_4 for qNMR or DSS-d_6 for qNMR, etc.

6.2 Notes on the description in the section "9.41 Reagents, Test Solutions" of the General tests for quantitative ^{1}H NMR or in the "Form-Std 2" and "Form-RelStd 2" of the Quality Standard for Reference Standard

6.2.1 Preparation of a qNMR sample solution

6.2.1.1 Sample

6.2.1.1.1 Information on a substance to be measured (analyte)

Essential information: Information on molecular mass used for calculation, hygroscopicity and sublimability (measured data/charts of water sorption-desorption, thermal analysis, etc), information on the status of dissolution in a solvent for qNMR (e.g., *X* mg of the analyte slowly dissolves in *Y* mL of a solvent).

6.2.1.1.2 Information on reference standard for qNMR

Essential information: Information on name, structural formula, constitution formula, molecular mass used for calculation, purity, and hygroscopicity and sublimability (water sorption-desorption, thermal analysis, etc), information on the status of dissolution in a solvent for qNMR (e.g., *X* mg of the reference standard slowly dissolves in *Y* mL of a solvent).

6.2.1.1.3 Information on reference standard for chemical shift (if necessary)

Name.

6.2.1.1.4 Information on solvent for qNMR

Name, deuteration rate.

6.2.1.2 Preparation of a sample solution

Information on the detailed preparation method of a sample solution (Amounts of a sample and a reference standard for qNMR taken, amount of added solvent for qNMR), a NMR tube, and reading at weighing.

6.2.1.3 Information on balance

Minimum weighing value (Refer to JIS K 0138: 2018, or USP "General chapter 41 balances" and US Pharmacopeia USP39-NF34, 2016 "General Information 1251 Weighing on Analytical Balances".

6.2.1.4 Information on weighing

Information on the temperature and humidity when weighing a sample, if the humidity is controlled, information on the method and the temperature/humidity.

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6.2.2 qNMR measurement

6.2.2.1 Qualification of instruments used (Confirm the qualification for qNMR measurement)

Describe the name of prepared solution, etc. used for the qualification of instruments (e.g., vinclozolin (CRM) and a solution of 1,4-BTMSB-d_4 (CRM) dissolved in DMSO-d_6)

6.2.2.1.1 Requirements of system suitability test (system repeatability, system performance, test for required detectability)

Perform the test using a sample solution. Describe the requirements referring to the JP "9.41 Reagents, Test Solutions".

6.2.2.2 Measurement conditions for qNMR

6.2.2.2.1 Target Nucleus

A target nucleus is a hydrogen nucleus in principle.

If target nuclei other than hydrogen are used, show information, such as the preparation method, detailed measurement conditions and analysis conditions, that can account scientifically the quantitative results of samples, referring to the notes on the description of ^{1}H quantitative NMR.

6.2.2.2.2 Magnitude of magnetic field (Instrument name when actual measurement)

^{1}H NMR: Not less than 400 MHz is recommended.

6.2.2.2.3 Digital resolution (Information when actual measurement)

For digital resolution 0.25 Hz or lower is recommended.

6.2.2.2.4 Measuring spectrum range (Spectral center and spectrum range when actual measurement)

Generally set the range that observe all signals of a sample as measuring spectrum range.

Spectrum range of 20 ppm or wider, including between -5 ppm and 15 ppm, is recommended. Further, it is desirable that the spectral center is set at the center of the signals that are used for quantitation.

6.2.2.2.5 Spinning (Information when actual measurement)

Spinning off is recommended.

6.2.2.2.6 Pulse angle (Information when actual measurement)

For pulse angle 90° is recommended.

6.2.2.2.7 Information on decoupling (Describe information of actual measurement, decoupling pulse sequence and offset value.)

Decoupling on is recommended.

6.2.2.2.8 Delay time (Information when actual measurement)

Set not less than 60 seconds generally. However, delay time may be set considering the target precision. In this case, show concretely the T_1 of the signal used for quantitation, and set the delay time at 5 to 7 times or more than the T_1 generally.

6.2.2.2.9 Number of Integrating times and SN ratio (Information when actual measurement)

Set the integrating times so that the SN ratio of the smallest signal used for quantitation is not less than 100 generally.

6.2.2.2.10 Number of dummy scans (Information when actual measurement)

Two or more times is recommended.

6.2.2.2.11 Measuring temperature (Information when actual measurement)

Set a constant temperature between 20°C and 30°C generally.

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6.2.2.3 Analytical conditions for qNMR

6.2.2.3.1 qNMR spectrum

Show the spectrum (including partial magnifications where necessary) of a qNMR sample solution.

Show the assignment of all signals of the analyte and the numbering on the structural formula.

6.2.2.3.2 Information of a signal to be quantitated

Show the reason for selecting the signals and the integral range (in ppm) of each signal used for quantification.

6.2.2.3.3 Data processing conditions

Show whether a window function, zero-filling, baseline correction, etc. are used in data processing.

Without using a window function, use of zero-filling and baseline correction is recommended.

6.2.2.3.4 Formula

Show the formula for calculating the content from signal intensities of the analyte and the reference standard for qNMR. Furthermore, if the content is calculated using multiple signals of the analyte, describe the fact.

Set the number of significant figures of the coefficients in the formula considering the target precision, and the notation should show the number of significant figures in the calculation of the content.

6.2.2.3.5 Result of quantitation and information of precision

Show the number of preparations (in principle, three times from weighing) and the number of qNMR measurements (in principle, three times discontinuously for each sample), and show the information accounting the precision of the quantitation statistically by describing the quantitation values obtained and its variation.

7. Others

7.1 Reference Standard and Reference Material

7.1.1 Definition of Reference Standard and Reference Material

Reference materials are the materials that are used as a standard in quantitative and qualitative measurement of chemical values, physical values or the amount of the biological activity of drugs etc., and in calibration and accuracy confirmation of apparatus used for tests of drugs etc. Reference Standards are reference materials prepared to have a certain quality necessary with regard to their intended use such as quality evaluation tests of drugs, and they are provided with the public assurance that the substances have suitable quality for specified use.

7.1.2 Name of Reference Standard

The name of Reference Standard used for quantitative tests is made to be “XXX RS” by attaching the term of “RS” to the name of an ingredient following “3.2.1 Japanese name of drug substance”. However, even if the source material of Reference Standard is a hydrate, do not attach the term, “hydrate”, to the name of the ingredient in principle.

Even if a non-proprietary name is named with putting a space, do not put a space to the name of the reference standard. *(Note: This is not related to the English version.*)

[Examples] Estradiol Benzoate RS
Aspoxicillin RS (Name of monograph is Aspoxicillin Hydrate.)
Cefuroxime Axetil RS (Name of monograph is Cefuroxime Axetil) *(Note: This is not related to the English version.)*

A Reference Standard having purpose other than quantitative tests only is named by adding the name of its purpose as necessary. A Reference Standard having more than one purpose is named in principle by adding the name of the purpose that requires more high quality or is more important.

[Examples]
Montelukast Sodium for Identification RS

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AAA for Purity RS
AAA Related Substance B for Purity RS
Montelukast for System Suitability RS

7.1.3 Amount of Reference Standard used

At the use of Reference Standard, try to reduce its amount within the range not impacting on the purpose of the test. For a chemical drug, the rough target of usage in the assay is generally between 20 mg and 50 mg.

7.1.4 Preparation of document concerning the establishment of Reference Standard

In establishing a reference standard used in the Assay for an active ingredient (chemicals, antibiotics, excipients, etc.) newly, prepare the document of Form-Std 1 to Std 6 according to Attachment 1.

In establishing a reference standard used in the Assay for a related substance newly, prepare the document of Form-RelStd 1 to RelStd 5 according to Attachment 2. These formats can also be applied to a reference standard used in the Assay for a marker compound and its purity has been determined using the quantitative NMR method.

In establishing XXX for System Suitability RS newly, prepare the document of Form-SysStd 1 to SysStd 5 according to Attachment 3.

Prepare the document Form-BioStd 1 to BioStd 4 according to Attachment 2 for a Reference Standard for a biological product.

7.1.5 Use of Reference Standard

JP Reference Standards are used for tests specified in Monographs and General Tests such as Assay, Identification, Purity, calibration of apparatus and suitability tests of analytical systems. These Reference Standards include materials with only one specific purpose and materials with multiple purposes.

7.1.6 Reference materials other than Reference Standard (reagent for assay, etc.)

For the chemical pharmaceuticals, the reference material used only for the quantitative test of preparations, such as the Assay, Dissolution or Content uniformity in Uniformity of dosage units, is generally established as the reference standard. If it is unavoidable to establish it as the reagent for assay, specify it as "XXX for assay" under "9.41 Reagents, Test Solutions", General Tests, Processes and Apparatus, and is described as "XXX for assay" in Official Monographs. Also, the reference materials used for assays for Quantitative Marker Constituents of Crude Drugs and Crude Drug Preparations can be established as the reagents for assay. In these cases, specify it as “XXX for assay” under “9.41 Reagents, Test Solutions”, General Tests, Processes and Apparatus, and describe as “XXX for assay” in Official Monographs.

The reference material used in the Identification by chromatography of preparations and crude drugs can be established as a reagent. In these cases, specify it under “9.41 Reagents, Test Solutions”, General Tests, Processes and Apparatus. The term, “for identification” or “for thin-layer chromatography”, etc. can be included in the name of reagent as appropriate.

7.2 Reagents, Test solutions, etc.

7.2.1 Reagents

The Reagent is used for the test of JP. When the reagent listed in the Japanese Industrial Standards (JIS) is used in JP, use JIS name in principle. Those described as standard reagent for volumetric analysis, special grade, first grade and for water determination or those to which the name of reagent is simply described conform to the specification and test method of the standard substance for volumetric analysis, special grade, first grade, and for water determination etc. of JIS reagent or those without grading, respectively. Describe additionally the JIS name when the JP reagent name is different from that of JIS.

When the drug listed in the Official Monographs is used as the reagent, such as the reference material for assay, use the name of the drug as the name of reagent in principle. However, if the substance with different number of hydrations exists, describe the number of hydration. Those specified as “Same as the namesake monograph” conform to the specifications in the monograph. For the reagents to which only the test method is described, simply apply the test methods of JP. Furthermore, before the drug in the monograph is established as the common reagent other than the Reference Standard, confirm the non-availability of an alternative reagent among JIS reagents, etc.

7.2.2 Test solutions

The Test solution (TS) is the solution prepared using the Reagent for the tests in JP.

7.2.3 Description of reagents and test solutions

Description method of the Reagent, Test solution and the Standard solution for volumetric analysis follows the "Japanese Pharmacopoeia Eighteenth Edition" and the followings.

7.2.3.1 Fundamental rules for names of reagent and test solution

1) When the drug listed in the Official Monographs is used as the reagent such as the reference material for assay, use the name of the drug as the name of reagent.
2) When the reagent met in JIS is used, use the JIS name as the name of the reagent.
3) When the reagent which does not correspond to 1) and 2) shown above is used, use the name complying with IUPAC nomenclature system as the name of the reagent in principle. In such case, use the Japanese name complying with the nomenclature of compounds specified by the Chemical Society of Japan as the name of the reagent.
4) When the reagent which does not correspond to 1) and 2) shown above is used, the traditional name used widely and the previous JIS reagent name can be used as the name of the reagent, regardless of the above stipulations in 3). However, only those that can be viewed at and obtained from the Japanese Standards Association (General Incorporated Foundation).
5) Designate the name of Test solution (TS) with the name of solute and solvent. However, when the solvent is water, do not include it in the name in principle. Furthermore, denominate excluding the description such as "N hydrate" and "anhydrous" giving no influence on its use after dissolution of the solute.
6) Designate the name of test solution using solvent to be described with concentration such as ethanol (99.5) as the name without concentration such as "XXX-ethanol TS" except for the case where omitting concentration may cause possible confusion.

7.2.3.2 Examples of description of name of reagent

1) Express the name of reagent and test solution in *Katakana* and *Kanji* character. (JIS reagent requires to express Japanese language by *Hiragana*, e.g., りん酸 (phosphoric acid), くえん酸 (citric acid), ひ素 (arsenic), etc., but the Japanese Pharmacopoeia does not adopt that policy.)
   (*Note: This rule is not related to the English version.*)
2) When *expressing* the name of reagent "XXX" by attaching parentheses, such as "XXX (100)", the figure in parentheses means the content (%) of the substance expressed by the molecular formula.

[Example] ethanol (95), ethanol (99.5), acetic acid (31), acetic acid (100), hydrogen peroxide (30), ammonia solution (28)

3) In the case where the drug in the Official Monographs is used as the reference material for assay, etc., use the name of the drug as the name of the reagent. When it is used as the reagent other than the reference material, follow the nomenclature of reagent in principle. However, the traditional name used widely may be used.
4) Describe reagents for special use as "XXX for YYY".

[Example] hexane for liquid chromatography

5) Express hydrochlorides of primary, secondary and tertiary amines "XXX 塩酸塩 (XXX hydrochloride)" and not as "塩化XXX"*. For inorganic salts, do not describe the number when the misunderstandings on the number of cations and anions are not generated. For organic compounds, describe the number of salts as much as possible.
   * (*Note: This rule is not related to the English version.*)

[Example] 1,3－フェニレンジアミン塩酸塩(1,3-phenylenediamine hydrochloride)

6) Use the symbol, D, L-, etc.

[Example] L-ascorbic acid

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7) Express the hydrate as "XXX N hydrate" (N is Chinese numeral)*, and if the number of waters is unknown, express as "XXX *n* hydrate". Express the anhydrous reagent simply as "XXX". However, use "anhydrous XXX" as appropriate to avoid confusion. For the hydrate of the reagent not listed in the Official Monographs, specify the number of the hydration water as far as possible.

* (*Note: This rule is not related to the English version.*)

[Example] disodium hydrogen phosphate dodecahydrate, phosphomolybdic acid *n* hydrate

8) Express the valency of an inorganic compound with Roman numeral as needed.

[Example] lead (II) oxide, lead (IV) oxide

7.2.4 Novel establishment of reagent and test solution

Use the reagents and test solutions already listed in JP as far as possible. Describe the preparation method of a simple solution and a solution used only in a certain monograph in each monograph if possible.

When establishing a reagent or test solution newly, make the specifications suitable for the intended purpose and/or use. If the quality level of the reagent is different from that already listed, use "for XX" to differentiate the name and content.

For the culture medium specified as Reagents, Test Solutions, specify the composition of the medium. However, in the case where the ingredients of the composition are publicly known, describe only the name of the culture medium. It is not necessary to set the specification of ingredients used for culture media.

7.2.5 Novel establishment of "XX for assay"

In the case where the drug in the monograph is used as the reference material for assay for the tests (identification, quantitative tests) in the monograph of preparations, establish "XX (name of drug of monograph) for assay" as a reagent.

Apply the monograph to the specification in principle, or tighten the acceptance criterion of content, etc. as appropriate.

In the case where "XX (name of drug of monograph) for assay" is used for quantitative tests by liquid chromatography but the purity test in the monograph of the drug substance has been specified by thin-layer chromatography, establish the test procedure suitable for the intended use as appropriate, such as changing the method of the Purity to the liquid chromatography under the same operating conditions as the quantitative tests.

7.2.6 Setting of new "standard solutions for the volumetric analysis" and "standard solutions"

When a new standard solution for volumetric analysis or a new standard solution is set, establish the traceability to the primary standard.

7.2.7 Setting of new Solid Supports/Column Packings for Chromatography

When an average pore diameter and a degree of cross-linkage, etc. are newly set, describe concrete establishment in the term of column under operating conditions in a monograph, not in "9.42 Solid Supports/Column Packings for Chromatography".

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