[Appendix 1]

General Notices

(Related to Article 2 Subparagraph 1)

General Notices

General Notices

1. General Considerations

1.1. This publication is the English version of the "대한민국약전 제 12 개정." and the English title is "The Korean Pharmacopoeia Twelfth Edition." These titles may be abbreviated to "약전 12" or "KP 12."

1.2. In the Korean Pharmacopoeia, "drugs" refers to those specified in the monograph, except for quasi-drugs. The "title names" of such drugs concern the Korean names or Korean common names adopted in the monograph. In the monograph, the English names and chemical names, or Latin names if necessary, are appended to the titles. General requirements for drugs are similarly applied to quasi-drugs.
The chemical name is written in English according to the nomenclature of the International Union of Pure (IUPAC) and Applied Chemistry, including the registry number of Chemical Abstract Service (CAS RN).

1.3. The conformity of drugs is determined according to the provisions given in the pertinent monograph, General Notices, General Requirements for Pharmaceutical Preparations, and the provisions of General Tests. However, the items of Description (except for color) and storage conditions under Packaging and storage in the monograph are given for informational purposes, but should not be taken as requirements. In the case of crude drugs, however, color, odor, and taste of the Description are viewed as indicating standards for conformity.

1.4. Drugs written in capital letters refer to the drugs that are recognized in KP 12.

1.5. When the labeled amount, labeling unit, or expiration date of a drug is specified in the monograph, these statements shall be shown on the container or package.

1.6. The names of drugs followed by molecular formulas or empirical formulas in parenthesis ( ) refer to chemically pure substances. Atomic masses adopted in KP 12 are calculated as per the table of "Standard Atomic Weights 2013." Molecular masses are indicated to two decimal places rounded from the third decimal.

1.7. When a drug or its ingredient used to manufacture the drug is derived from animals, the animals must be healthy in principle, unless otherwise specified.

1.8. The following symbols are used for the principal units in this Pharmacopoeia.

Measurements	Units	Symbol
Length	meter	m
	centimeter	cm
	millimeter	mm
	micrometer	㎛
	nanometer	nm
	ångström	Å
Mass	kilogram	kg
	gram	g
	milligram	mg
	microgram	μg
	nanogram	ng
	picogram	pg
	dalton	Da
	kilodalton	kDa
Volume	liter	L
	deciliter	dL
	milliliter	mL
	microliter	μL
Temperature	degree Celsius	℃
Angle	degree	°
Area	square centimeter	cm^2
Force	newton	N
Viscosity	pascal second	Pa·s
	millipascal second	mPa·s
	square millimeter per second	mm^2/s
Amount of Substance	mole	mol
	millimole	mmol
	micromole	㎛ol
	equivalent	Eq
	milli equivalent	mEq
	osmole	Osmol
	milliosmole	mOsmol
Concentration	mass percent	%
	volume percent	vol%
	mass per volume percent	w/v%
	mass parts per million	ppm
	mass parts per billion	ppb
	volume parts per million	vol ppm
	mole per liter	mol/L
	millimole per liter	mmol/L
Pressure	pascal	Pa
	kilopascal	kPa
	millimeter of mercury	mmHg
Electrical Units	volt	V
	millivolt	mV
	hertz	Hz
	kilohertz	kHz
	megahertz	MHz
	electron volt	eV
	kiloelectron volt	keV
	megaelectron volt	MeV
	microsiemens per centimeter	$\mu S \cdot cm^{-1}$
Radiation	becquerel	Bq
	kilobecquerel	kBq
	megabecquerel	MBq
	gigabecquerel	GBq
	millisievert	mSv
	microsievert	μSv
	curie	Ci
	millicurie	mCi
	microcurie	μCi
	nanocurie	nCi

Measurements	Units	Symbol
Other	revolutions per minute	rpm
	kaiser (wavenumber)	cm^{-1}
	endotoxin unit	EU
	colony forming unit	CFU
	nephelometric turbidity unit	NTU
	formazin turbidity unit	FTU
	chemical shift in Nuclear Magnetic Resonance Spectroscopy	ppm

The following major prefixes in the International System of Units can be used.

Name	Symbol	Factor	Name	Symbol	Factor
giga	G	10^{9}	milli	m	10^{-3}
mega	M	10^{6}	micro	μ	10^{-6}
kilo	k	10^{3}	nano	n	10^{-9}
deci	d	10^{-1}	pico	p	10^{-12}
centi	c	10^{-2}	femto	f	10^{-15}

1.9. The "unit" used for expressing the potency of a drug is considered as the quantity of the drug. Usually, it is expressed by a quantity of reference standard which shows a definite biological activity, and differs according to each drug. The units are determined, in principle, by comparison with each reference standard through biological methods. The term "unit" used for the drugs listed in the KP refers to the compendial unit. However, the potency of antibiotics is expressed as "mass (potency)" or "unit," and determined by comparison through the biological and physicochemical method with each reference standard.

1.10. The temperature in the test or storage is described in specific figures in principle. However, the standard temperature, ordinary temperature, room temperature, and lukewarm refer to 20 °C, 15 to 25 °C, 1 to 30 °C and 30 to 40 °C, respectively. A cold place, unless otherwise specified, should be a place having a temperature of 1 to 15 °C. The temperatures of cold water, lukewarm water, warm water, and hot water refer to below 10 °C, 30 to 40 °C, 60 to 70 °C and about 100 °C, respectively.

The term "heated solvent" or "hot solvent" means a solvent heated at an almost its boiling point, and "warmed solvent" or "warm solvent" usually means a solvent heated to a temperature between 60 °C and 70 °C. The term "heat in a water bath" indicates, unless otherwise specified, boiling status in a water bath or heating with a steam at about 100 °C. Cold extraction and warm extraction are usually performed at 15 to 25 °C and 35 to 45 °C, respectively.

1.11. Unless otherwise specified in the test of the monograph, when a temperature is expressed as a single value, the tolerance is ± 3 °C of a given value; when a pressure, length, or time is expressed as a single value, its tolerance is ± 10%.

1.12. To measure the number of drops, a device which weighs 0.90 to 1.10 g when dropping 20 drops of water at 20 °C should be used.

1.13. For indicating a name of solution, the name of solute is followed by the name of solvent, and the one without the solvent name means aqueous solution.

1.14. The "Acidity or alkalinity" of a solution, unless otherwise specified, is determined by litmus paper. To indicate these properties more precisely, pH values are used.

1.15. The terms in the following table are used to express the degree of "coarseness" or "fineness" of a drug.

Sieve No.	Names of the powders passed through the sieve
4 (4750 μm)	Coarse cutting
6.5 (2800 μm)	Medium cutting
8.6 (2000 μm)	Fine cutting
18 (850 μm)	Coarse powder
50 (300 μm)	Medium powder
100 (150 μm)	Fine powder
200 (75 μm)	Very fine powder

1.16. The concentration of a solution expressed as (1 in 10) means that 1 part by weight of a solid shall be dissolved in, or 1 part by volume of a liquid shall be diluted with, a sufficient quantity of the solvent or diluent to make the volume of the finished solution 10 parts by volume. An expression such as "(5:2:1)" means that the respective numbers of parts, by volume, of the designated liquids shall be mixed.

1.17. The reagents specified in the General Tests should be used for the test of drugs, unless otherwise specified, and the water should be suitable for performing the relevant test, which is not containing any substance that would interfere with the test. Purified water and water for injection used in the manufacture of preparations should be suitable for the monograph.

1.18. The term "in vacuum" denotes exposure to a pressure of NMT 2.0 kPa, unless otherwise indicated.

1.19. The term "weigh accurately" means to weigh the mass down to 0.1 mg, 0.01 mg, or 0.001 mg according to the minimum number of decimal places to be added, and the term "weigh exactly" means to weigh to the given decimal places.

1.20. In a test of a drug, to obtain n-digit value, (n+1) decimal place should be obtained and then rounded up.

For example, the expression "NLT 95.0% and NMT 105.0%" specified in the Assay means that the content determined by the assay should be between 94.95% and 105.04% to conform to the specification.

1.21. Unless otherwise specified, all tests of drugs should be performed at ordinary temperature, and the results should be observed immediately after the operations. However, the judgment which is affected by the temperature should be based on the condition at standard temperature.

1.22. The term "immediately" used in a test of a drug means that the next procedure is to be performed within 30 seconds after the preceding one is done.

1.23. In the Description section, the term "white" is used to indicate white or almost white, and "colorless" to indicate colorless or almost colorless. Unless otherwise specified, the color of the solid drug is observed by placing 1 g on a sheet of white paper or in a watch glass placed on white paper. A liquid drug is put into a colorless test tube of 15-mm internal diameter and is observed in front of a white background with a depth of 30 mm. For the test of clarity of a liquid drug, the above procedure is applied with either a black or white background. For the fluorescence of liquid drug, a black background is used when observing.

1.24. In the Description section, the term "odorless" or "no odor" is used to indicate odorless or practically odorless. Unless otherwise specified, the smell should be tested by placing 1 g of a solid drug or 1 mL of a liquid drug in a beaker.

1.25. In the Description section, the solubility of a drug is indicated by the terms in the following table. Unless otherwise specified, "solubility" means the degree of dissolution of a powdered drug (in the case of a solid form) within 30 minutes, put in a solvent at 20 ± 5 °C, and shaken vigorously for 30 seconds at 5-minute intervals.

Descriptive term	Amount of solvent required for dissolving 1 g or 1 mL of solute	
Very soluble		less than 1 mL
Freely soluble	NLT 1 mL	and less than 10 mL
Soluble	NLT 10 mL	and less than 30 mL
Sparingly soluble	NLT 30 mL	and less than 100 mL
Slightly soluble	NLT 100 mL	and less than 1000 mL
Very slightly soluble	NLT 1000 mL	and less than 10 L
Practically insoluble	NLT 10 L	

1.26. In the test of a drug, the description "drugs dissolve or miscible in the solvent" indicates that it dissolves in or mixes with, in arbitrary proportion, in the solvent to form a clear solution or mixture, so that the presence of fibers, etc., can't be seen or very few in extremely minute quantities.

1.27. "Identification" refers to the test to identify the drug or the active pharmaceutical ingredient (API), etc. in it based upon a specific property. However, in the case of radiopharmaceuticals, it is necessary to identify drugs or radionuclides contained in drugs based on the properties of the radiation emitted by the radionuclides or to identify drugs based on their properties.

1.28. "Purity" is for testing the impurities in drugs as well as specifying the purity of the drug with the other test items in the monograph, and usually limiting the kind and quantity of the impurities. The impurities to be tested are those supposed to contaminate the drug during the manufacture or storage of that drug, as well as hazardous ones, such as heavy metals, arsenic, and so on. If the foreign substances are expected to have been used or added, this test is necessary. However, for radiopharmaceuticals, radiochemical impurities refer to heterogeneous compounds containing the same radionuclide, and heteronuclides refer to radionuclides other than the radionuclide concerned.

1.29. The term "constant mass" in drying or ignition, unless otherwise specified, means that the difference in mass after an additional hour of drying or ignition is NMT 0.10 percent of the previous mass of the dried substance or ignited residue. In crude drugs, this percent is set to NMT 0.25 percent. However, when the difference does not exceed 0.5 mg in a chemical balance, 50 μg in a semimicrobalance, and 5 μg in a microbalance, it is considered a constant mass.

1.30. "Assay" is the test to determine the composition, the content of the ingredients, and the potency unit of a drug by physical, chemical, or biological methods. However, for radiopharmaceuticals, it is to measure the radioactivity of a drug through physicochemical methods or to calculate specific radioactivity by measuring the composition, the content of the ingredients, and the potency unit of a drug through physicochemical methods.

1.31. The word "about" added to sample quantity in the assay means that the weighed quantity of the sample may deviate within ± 10% of the described quantity. And the word "previously dried" in the sample indicates drying under the same conditions as described in the section of Loss on drying in the monograph.

1.32. The test methods of the Korean Pharmacopoeia can be replaced by alternative methods if they have better accuracy and precision. However, where there is any doubt in the result, the final decision shall be made based on the compendial method.

1.33. The details of the biological test methods may be changed, provided that they do not affect the essential qualities of the test.

1.34. When handling and testing the drugs, special attention must be paid to safety management, including not to inhale or to contact with the drugs or reagents, given their properties.

2. Preparations

2.1. In the content of pharmaceutical preparations, for example, the expression “contains NLT 95.0% and NMT 105.0% of the labeled amount of pure products,” indicates that it is usually prepared to contain the labeled amount of the chemically pure substance or a substance corresponding thereto, and that it is quantitatively determined within the above range. However, for radiopharmaceuticals, the expression “contains NLT 90.0% and NMT 110.0% of the labeled radioactivity at the time of testing” indicates that the radioactivity is within the range of 90.0 to 110.0% of the labeled radioactivity at the time of testing when the radioactivity is quantified.

2.2. Excipients are other than API contained in preparations, which are used to increase the utility of the preparation, facilitate the formulation, promote the product's stabilization, improve the appearance of products, and so on. For these purposes, suitable excipients such as diluents, stabilizing agents, antimicrobial preservative, buffering agent, flavor enhancer, suspending agents, emulsifier, flavors and fragrance, solubilizing agents, coloring agents, and viscosity-increasing agent may be added. The excipients used, however, should not show direct pharmacological effect upon the dosage but be safe, and should not change the therapeutic efficacy or interfere with the test of the preparations.

2.3. “Vegetable oils” used in preparations usually indicate the edible vegetable oils listed in the monograph. However, “starch” in pharmaceutical preparations can be any kind of starch listed in the monograph, unless otherwise specified. Ethanol specified as vol% is prepared by adding purified water or “Water for Injection” to be the specified vol%.

2.4. Functions to control the transfer of API in the body can be added to pharmaceutical preparations to control the onset and duration of therapeutic actions and reduce side effects. However, these preparations should be suitable for the test of preparation properties, such as dissolution test, etc., unless otherwise specified.
In addition, the functional modification of the release rate prescribed in the monograph should be indicated on the package insert and the direct container or packaging of the preparation that control the release rate, unless otherwise specified.

2.5. Preparations for oral application include immediate-release preparations and modified-release preparations, depending on their release profile. Immediate-release preparations have a release pattern of active pharmaceutical ingredients, which is not intentionally altered and generally depends on the intrinsic physicochemical properties of the active pharmaceutical ingredients. Modified-release preparations have a release pattern of active pharmaceutical ingredients, which is suitably modified for the desired purpose by means of a specific formulation design and preparation method. They include delayed-release preparations and extended-release preparations. Delayed-release preparations are designed to release the active pharmaceutical ingredients in the intestinal environment rather than in the gastric environment to prevent degradation or decomposition of the active pharmaceutical ingredients or to reduce the irritating effect of the active pharmaceutical ingredients in the stomach. Delayed-release preparations are generally prepared by applying enteric coating agent. Extended-release preparations are aimed at controlling the release rate, time and sites of active pharmaceutical ingredients to decrease dosing numbers and/or reduce side effects. They are generally prepared by using suitable sustained release modifying agent that prolong the release of active pharmaceutical ingredients.
Granules, Powders, Tablets, Capsules or Pills of preparations for oral application can be coated with suitable coating agents, such as sugars, sugar alcohols or high molecular weight polymers to facilitate ingestion or prevent degradation of active pharmaceutical ingredients.

2.6. Unless otherwise specified, preparations are preferably stored at room temperature. Preparations must be stored by shading the light if the quality is affected from the light. However, unless otherwise specified, radiopharmaceutical preparations are stored at room temperature, protected from light, if possible. Liquids and liquid injections to be stored in a cold place should avoid freezing unless otherwise specified.

2.7. To secure the quality, requirements to be followed during the manufacturing process, in addition to the specifications if necessary, are indicated in the Method of preparation section of the monograph. It is important to attend to proper management of raw materials/ingredients, manufacturing processes, and intermediates for each drug product, even if there is no method of preparation section in the monograph.

2.8. Drugs in the Korean Pharmacopoeia are, in principle, managed in accordance with the Residual Solvents of General Tests unless otherwise specified.

2.9. Sterility means that no microorganisms are present, therefore the target microorganisms cannot be detected by a specified method. Sterilization refers to killing or removing all microorganisms in a substance to be sterilized. Aseptic processing refers to a procedure performed in a controlled manner to maintain sterility.

2.10. Sterile preparations have been verified to be sterile. The basic manufacturing methods for sterile preparations include terminal sterilization and aseptic processing.

2.11. Non-sterile pharmaceutical preparations should also avoid contamination and the growth of microorganisms, and the Microbiological Examination of Non-sterile Products should be performed if necessary.

2.12. Some tests in the monograph may be omitted if necessary, e.g. release test, when the manufacturing process validation and the records of inspection of appropriate process control and quality control can always ensure that its quality conforms to the Korean Pharmacopoeia.

3. Crude Drug and Crude drug Product

3.1. "Crude drugs" in the monograph include medicinal parts obtained from plants and animals, cell inclusions, secretions, extracts, or minerals.

3.2. Crude drugs are usually categorized as the whole crude drugs, cut crude drugs or powdered crude drugs. Whole crude drugs are prepared by drying or simply processing medicinal parts, as specified in the monograph. Cut crude drugs are prepared by cutting or crushing the whole crude drugs into small pieces or blocks, and also coarse, medium, or fine cuts. Powdered crude drugs are coarse, medium, fine, or very fine powder made from the whole crude drugs or cut crude drugs. Unless otherwise specified, they should conform to the specifications of the whole crude drugs used as source materials.

3.3. Unless otherwise specified, dried crude drugs are used. Drying is usually carried out at a temperature not exceeding 60 ℃.

3.4. Crude drugs shall be kept clean and hygienic by removing contaminants, impurities, or other foreign substances from fungi, insects or other animals as possible throughout the processes, including harvest, processing, packaging, and distribution.

3.5. The origin of crude drugs is considered as the criterion for judging suitability. Statements such as "other congeneric plants," "other congeneric animals," "other allied plants," "other allied animals," etc. in the origin of crude drugs usually indicate source plants or source animals which may be used as materials for crude drugs containing the same ingredients and having same pharmacological activities.

3.6. Description of crude drugs in the monograph usually includes statements of characteristic properties of the crude drug derived from its typical source plant, animal, or mineral to be considered as the criterion for judging suitability. The values given therein are represented as approximate values, except those obtained by microscopic observation.

3.7. Powered crude drugs do not contain fragments of tissues, cells, cell inclusions, or other foreign matters that were not included in the whole crude or cut crude drugs.

3.8. Powdered crude drugs specified separately may be mixed with diluents to achieve proper content and potency.

3.9. Crude drugs are stored under protection from moisture and insect damage unless otherwise specified. To prevent insect damage, suitable fumigants may be used to preserve crude drugs, but they should volatilize readily at room temperature, be harmless at the usual dosage of the crude drugs, and should not change the therapeutic efficacy of the crude drugs or interfere with the testing.

3.10. Unless otherwise specified, crude drugs are preserved in well-closed containers.

4. Radiopharmaceuticals

4.1. For radiopharmaceuticals, "at the time of testing" refers to the indicated date or time, i.e., the date or time when the drug has the labeled radioactivity.

4.2. For radiopharmaceuticals, the Bacterial Endotoxins or the Pyrogen of Injections may be performed after the radioactivity decayed after release unless otherwise specified. Injections, containing a nuclide with a half-life of less than 240 hours, which are manufactured by a sterilization procedure in which sterilization efficacy has been confirmed by testing with an appropriate indicator bacterium or chemical indicator, can be released before the completion of the Sterility test that started on the manufacture date.

4.3. For radiopharmaceuticals, the containers shielding the radiation must have adequate shielding capacity. The exterior of the container should not be easily damaged. The maximum radiation dose rate on the exterior of container shall be as follows:

1) Less than 2 mSv per hour on the exterior surface of the container. However, in the case of exclusive transportation container, it shall be less than 10 mSv per hour.
2) Less than 0.1 mSv per hour at a place 1 m away from the exterior surface of container. However, it is not applicable to exclusive transportation container.

4.4. For radiopharmaceuticals, a radioactive pictogram must be indicated on the direct container or package of radiopharmaceuticals and the word "radiopharmaceuticals" must be indicated on its upside. However, the radioactive labeling can be omitted if the drug contains radionuclides less than the amount of specified in the following table:

Types of isotopes emitting radiation	Quantity
Strontium-90 and alpha ray emitters	3.7 kBq
Physical half-life is greater than 30 days (except for hydrogen-3, beryllium-7, carbon-14, sulfur-35, iron-55, iron-59, and strontium-90, and alpha ray emitters)	37 kBq
Physical half-life is NMT 30 days (except for fluorine-18, chromium-51, germanium-71, thallium-201, and alpha ray emitters), sulfur-35, iron-55, and iron-59	370 kBq
hydrogen-3, beryllium-7, carbon-14, fluorine-18, chromium-51, germanium-71, and thallium-201	3.7 MBq

※ If there are two or more radionuclides, the quantity of each radionuclide in the left column of this table is set as the one of radionuclides for which the sum of the ratios to the quantities in the right column is 1.

5. Container and Packaging

5.1. The "container" is a thing that drugs are put in, and the things that are used to close the containers are also considered part of containers. The containers should have no physical and chemical activity affecting the specified Description and quality of a drug.

5.2. A "well-closed container" is a container that can protect the contents from contamination by extraneous solids and from loss of the drug under the ordinary conditions of handling or storag. For the container specified as a well-closed container, a tight container may be used.

5.3. A "tight container" is a container that can protect the contents from contamination by extraneous solids or liquids and from loss of the drug, and from efflorescence, deliquescence, or evaporation under the ordinary conditions of handling or storage. For the container specified as a tight container, a hermetic container may be used.

5.4. A "hermetic container" is a container that can prevent the invasion of any gas or microorganism under the ordinary conditions of handling or storage.

5.5. The term "light-resistant" means to protect the drug from the influence of light under customary conditions of handling, transportation, and storage by preventing the transmission of light affecting the specified Description and quality of the drugs. In the case of single-dose preparations, the packaging that can prevent the transmission of light into a single direct container is considered as light-resistant.

5.6. Containers and packaging for preparations must be suitable for proper use and extra safety as well as for maintaining the quality of the preparations. Deoxidizing agents or a material with low gas permeability may be used for the container to maintain the quality of preparations from atmospheric oxygen, etc. For preparations susceptible to moisture, desiccants or materials with low gas permeability may be used for the containers. For preparations susceptible to evaporation of water, containers made of materials with low water vapor permeability may be used.

5.7. It is important to sufficiently review the suitability of the container and packaging of the preparation in the development phase to ensure the quality requirements of the preparation during the shelf-life (expiration date). In this review of the suitability of the packaging according to the characteristics of the preparation, items for proper quality control are established, such as specifications and tests of the final product, in-process control, and evaluation of data used for product packaging, etc. The adequacy of the items is finally determined by the stability test of the preparation.

5.8. The suitability of packaging includes factors of the protection of the preparation, the compatibility of the preparation and packaging, the safety of packaging materials, and the additional performance during administration.

5.9. When changing the container and packaging of the preparation, it is necessary to review the above items. In addition, appropriate tests must be performed to determine whether unexpected changes in packaging affect the quality of the preparation.

5.10. For the containers and packaging for injections, the suitability of packaging should be reviewed first based on the Glass Containers for Injections, the Plastic Containers for Pharmaceutical Use, the Elastomeric Closures for Injections, the Packaging Integrity, the Photostability, and the tests described in the monograph, and then the quality control items should be established.