Notes:

1) For products to be administered by mass or by units, the endotoxin limit should be decided based on the labeled amount of the principal drug.

2) Sixty kg should be used as the average body mass of an adult when calculating the maximum adult dose per kg.

3) The pediatric dose per kg body mass should be used when this is higher than the adult dose.

4) The K values for the intravenous route are applicable to drugs to be administered by any route other than those shown in the table.

3. Disinfection and Sterilization Methods

Disinfection and Sterilization Methods are applied to kill microorganisms in processing equipment/utensils and areas used for drug manufacturing, as well as to perform microbiological tests specified in the monographs, and so differ from "Terminal Sterilization" and "Filtration Method" described in "Terminal Sterilization and Sterilization Indicators". The killing effect on microorganisms or the estimated level of sterility assurance is greatly variable, so the conditions for disinfection and sterilization treatment must be chosen appropriately for each application. Generally, the following methods are to be used singly or in combination after appropriate optimization of operation procedures and conditions, in accordance with the kind and the degree of the contaminating microorganisms and the nature of the item to which the methods are applied.

The validation of sterilization in accordance with Terminal Sterilization and Sterilization Indicators is required when the methods are applied to the manufacturing processes of drug products.

1. Disinfection methods

These methods are used to reduce the number of living microorganisms, but do not always remove or kill all microorganisms present. Generally, disinfection is classified into chemical disinfection with the use of chemical drugs (disinfectants) and physical disinfection with the use of moist heat, ultraviolet light, and other agents.

1-1. Chemical disinfection

Microorganisms are killed with chemical drugs. The killing effect and mechanisms of a chemical drug differ depending on the type, applied concentration, action temperature, and action time of the chemical drug used, the degree of contamination on the object to be disinfected, and the species and state (e.g., vegetative bacteria or spore bacteria) of microorganisms.

Therefore, in applying the method, full consideration is required of the sterility and permissible storage period of the prepared chemical drug, the possibility of resistance of microorganisms at the site of application, and the effect of residual chemical drug on the product. In selecting a suitable chemical drug, the following items should be considered in relation to the intended use.

1) The antimicrobial spectrum
2) Action time for killing microorganisms
3) Action durability
4) Effect of the presence of proteins
5) Influence on the human body
6) Solubility in water
7) Influence on the object to be disinfected
8) Odor
9) Convenience of use
10) Easy disposability
11) Influence on the environment at disposal
12) Frequency of occurrence of resistance

1-2. Physical disinfection

Microorganisms are killed without a chemical drug.

(i) Steam flow method

Microorganisms are killed by direct application of steam. This method is used for a product which may be denatured by the moist heat method. As a rule, the product is kept in flowing steam at 100°C for 30 - 60 minutes.

(ii) Boiling method

Microorganisms are killed by putting the object in boiling water. This method is used for a product which may be denatured by the moist heat method. As a rule, the product is put in boiling water for 15 minutes or more.

(iii) Intermittent method

Microorganisms are killed by heating for 30 - 60 minutes repeatedly, three to five times, once a day in water at 80 - 100°C or in steam. This method is used for a product which may be denatured by the moist heat method. There is another method called the low temperature intermittent method with repeated heating at 60 - 80°C. During the intermission periods between heating or warming, a suitable temperature for the growth of microorganisms of 20°C or higher, must be maintained.

(iv) Ultraviolet method

As a rule, microorganisms are killed by irradiation with ultraviolet rays at a wavelength of around 254 nm. This method is used for products which are resistant to ultraviolet rays, such as smooth-surfaced articles, facilities, and equipment, or water and air. This method does not suffer from the occurrence of resistance, which is observed in chemical disinfection, and shows a killing effect on bacteria, fungi, and viruses. It must be taken into consideration that direct ultraviolet irradiation of the human body can injure the eyes and skin.

2. Sterilization methods

2-1. Heating methods

In these methods, the heating time before the temperature or pressure reaches the prescribed value differs according to the properties of the product, the size of the container, and the conditions. The duration of heating in conducting these methods is counted from the time when all the parts of the product have reached the prescribed temperature.

(i) Moist heat method

Microorganisms are killed in saturated steam at a suitable temperature and pressure. This method is generally used for heat-stable substances, such as glass, porcelain, metal, rubber, plastics, paper, and fiber, as well as heat-stable liquids, such as water, culture media, reagents, test solutions, liquid samples, etc. As a rule, one of the following conditions is used.

115 - 118°C for 30 minutes
121 - 124°C for 15 minutes
126 - 129°C for 10 minutes

(ii) Dry-heat method

Microorganisms are killed in dry-heated air. This method

is generally used for heat-stable substances, such as glass, porcelain, and metal, as well as heat-stable products, such as mineral oils, fats and oils, powder samples, etc. This method is generally conducted in the way of direct heating by gas or electricity or circulating heated air. As a rule, one of the following conditions is used.

160 - 170°C for 120 minutes
170 - 180°C for 60 minutes
180 - 190°C for 30 minutes

2-2. Irradiation methods

(i) Radiation method

Microorganisms are killed by gamma-rays emitted from a radioisotope or electron beam and bremsstrahlung generated from an electron accelerator. This method is generally used for radiation-resistant substances such as glass, porcelain, metal, rubber, plastics, fiber, etc. The dose is decided according to the material properties, and the degree of contamination of the product to be sterilized. Special consideration is necessary of the possibility of qualitative change of the product after the application of the method.

(ii) Microwave method

Microorganisms are killed by the heat generated by direct microwave irradiation. This method is generally used for microwave-resistant products such as water, culture media, test solutions, etc. As a rule, microwave radiation with a wavelength of around 2450 ± 50 MHz is used.

2-3. Gas methods

Microorganisms are killed by a sterilizing gas. Suitable gases for killing microorganisms include ethylene oxide gas, formaldehyde gas, hydrogen peroxide gas, chlorine dioxide gas, etc. Temperature, humidity, the concentration of gas, and the exposure time differ in accordance with the species of gas used. As sterilizing gases are generally toxic to humans, full consideration is required of the environmental control for the use of gases and the concentration of residual gas. In some of the gas methods, it may be difficult to measure or estimate quantitatively the killing of microorganisms.

2-4. Filtration method

Microorganisms are removed by filtration with a suitable filtering device. This method is generally used for gas, water, or culture media and test solutions containing a substance that is water-soluble and unstable to heat. As a rule, a filter having a pore size of 0.22 μm or smaller is used for the sterilization. However, in this method, a filter with a pore size of 0.45 μm or smaller is permitted to be used.

4. Guideline for Residual Solvents, Residual Solvents Test, and Models for the Test in Monographs

1. Guideline for Residual Solvents

Refer to the Guideline for Residual Solvents in Pharmaceuticals (PAB/ELD Notification No.307; dated March 30, 1998).

The acceptable limits of residual solvents recommended in the Guideline were estimated to keep the safety of patients. The levels of residual solvents in pharmaceuticals should not exceed the limits, except for in a special case. Accordingly, pharmaceutical manufacturers should assure the quality of their products by performing the test with the products according to the Residual Solvents Test, to keep the limits recommended in the Guideline.

2. Residual Solvents Test

Method—Perform the test as directed in the Residual Solvents Test under the General Tests, Processes and Apparatus.

International harmonization—The test may also be performed according to the Residual solvents in the EP or the Organic volatile impurities in the USP. Even in this case, Monographs should be described in the JP style.

3. Models for the Test in Monographs

The following are typical examples for the test in Monographs, but these do not necessarily imply that other suitable operating conditions can not be used. It is important to prepare (draft) monographs according to the Guideline for the Preparation of the Japanese Pharmacopoeia.

1) A model for test item, amounts of test sample and reference standard (reference substance), preparation of the sample solution and the standard solution, injection amount for gas chromatography, calculation formula, and preparation of the internal standard solution

Residual solvents (or name of the solvent)—Weigh accurately about 0.200 g of △△△ (name of the substance to be tested), add exactly 5 mL of the internal standard solution to dissolve, add water to make exactly 20 mL, and use this solution as the sample solution. If necessary filter or centrifuge. Separately, weigh exactly 0.10 g of ○○○ reference substance (name of the solvent), put in a vessel containing 50 mL of water, and add water to make exactly 100 mL. Pipet 5 mL of this solution, and add water to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 5 mL of the internal standard solution and 20 mL of water, and use this solution as the standard solution. Perform the test with 1 μL each of the sample solution and the standard solution as directed (in the head-space method) under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of △△△ (name of the substance to be tested) to that of the internal standard of each solution, respectively. The amount of △△△ should be not more than × × ppm.

$$\text{Amount of ○○○ (μg)} = \text{amount of ○○○ reference substance (μg)} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of △△△ in ▽▽▽ (name of solvent) (1 in 1000).

2) Models for operating conditions for a head-space sample injection device

Operating conditions (1) for the head-space sample injection device—

Equilibration temperature for inside vial	A constant temperature of about 80°C
Equilibration time for inside vial	60 minutes
Transfer-line temperature	A constant temperature of about 85°C
Carrier gas	Nitrogen
Pressurisation time	30 seconds
Injection volume of sample	1.0 mL