**General Rules**

1 These standards (”Minimum Requirement for Veterinary Biological Products”）specify the manufacturing methods, properties, quality, storage, and other matters for veterinary biological products listed in the monograph of drugs (hereafter referred to as “monographs”). These standards are abbreviated to “veterinary biological standards” in this document. Monographs include bulk material or final bulk that serve as intermediate products.

2 The *Japanese Pharmacopoeia* is specified by the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Law No. 145, 1960, hereafter referred to as "Law"), and the Japanese Industrial Standards are specified by the Industrial Standardization Law (Law No. 185, 1949).

3 “Standard names” imply names listed in the monograph of drugs.

For bulk material or final bulk, however; standard names shall be specified by appending “bulk material” or “final bulk” to the names listed in the respective monograph of drugs. Standard names are considered nonproprietary names when applied to Article 50 of the Law.

4 Veterinary biological products are to be judged according to the provisions given in the General Rules, pertinent monograph, and the provisions of the General Tests. For bulk material or final bulk that served as intermediate products in the pertinent monograph, these products shall be judged according to the rules specified in the sections related to bulk material or final bulk.

5 The details of the manufacturing methods and test items in the test methods may be changed under the condition in which products manufactured after changes are made are equal to or better than those manufactured in a specified manner only when such changes are approved as specified in Article 14, Article 19 (2), Article 23 (2)-5, or Article 23 (2)-17 of the Law.

6 Standard names enclosed in single quotation marks (‘ ’) indicate that the properties and quality conform to those specified in these standards; however, the standard names shown in the title of pertinent monograph shall not be enclosed in these marks, and those enclosed in double quotation marks (“ ”) indicate substances that exhibit specific biological activities.

7 The following abbreviations are used as main units of measurement:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Centimeter | cm |  | Kilogram | kg |
| Millimeter | mm |  | Gram | g |
| Nanometer | nm |  | Milligram | mg |
| Square centimeter | cm2 |  | Microgram | μg |
| Liter | L |  | Mole per liter | mol/L |
| Deciliter | dL |  | Pascal | Pa |
| Milliliter | mL |  | Gravity acceleration | *G* |
| Microliter | μL |  |  |  |

8 Mass percent, mass per volume percent, and volume percent shall be expressed as %, w/v% and vol%, respectively.

9 The Celsius scale is used for temperature measurement and “°C” is added after Arabic numerals.

10 Solutions without a solvent name indicate water solutions.

11 “Diluent” indicates an attached diluent or diluting solution approved as suitable for dissolving of the relevant product.

12 For veterinary biological products freeze-dried or intended to be dissolved for use whose label instructions state “Dissolve with diluent” only, these products shall be dissolved using diluent according to the method stated on the container.

13 Unless otherwise specified, pharmaceuticals or chemical agents that are listed in the *Japanese Pharmacopoeia* (JP) and that are used to manufacture drugs in the monographs shall comply with the JP requirements, whereas those not listed in the JP but specified in the Japanese Industrial Standards shall comply with their specifications depending on the purpose of use.

14 Inactivator and stabilizer specified by the term, for example, “use suitable agents” in the monograph of drugs shall be safe for use at the usual amount used and shall not inhibit the beneficial effects of the drug or interfere with pharmaceutical tests.

15 The actual amount of drugs in the monographs and attached diluents shall be sufficient for collecting the labeled amount and sufficient for the administration of the labeled dose.

16 “Original strain” indicates a virus strain, strain, or coccidia strain specified as the strain used for production in the monograph of drugs.

“Original virus,” “original bacteria,” or “original coccidia” indicates a passaged original strain used for the production of the seed virus, seed bacteria, or seed coccidia for vaccines. It is passaged according to the specified method in the part the vaccines in monograph of drugs or in the specifications and has the same property as that of the original strain.

“Seed virus,” “seed bacteria,” or “seed coccidia” indicates a passaged original strain directly used for production of vaccine. It is passaged according to the specified method in the monograph of drugs and has the same property as that of the original strain.

17 “Primary cultured cells” indicate cultured cells obtained from appropriate tissues through trypsin digestion and etc. and basically having the same property as that of the original cells.

“Passaged cells” indicate cultured cells having the continuous propagation ability.

18 “Seed lots” indicate homogeneous suspensions of specific viruses, bacteria, and cells etc. obtained from single cultures and stored under proper conditions to maintain their genetic properties.

19 “Seed lot product” indicates a vaccine produced using seed lots.

20 “Master seed” indicates a virus strain used for the production of seed lot products specified in the monograph of drugs and passaged not more than approved passages and it is permanently stored as a virus strain (hereafter referred to as “master seed virus”), as a bacterial strain (hereafter referred to as “master seed bacteria”), and as a coccidia strain (hereafter referred to as “master seed coccidia”).

“Working seed” indicates a virus strain derived from the master seed and not directly used for manufacturing the products (hereafter referred to as “working seed virus”), a bacteria strain derived from master seed and not directly used for manufacturing the products (hereafter referred to as “working seed bacteria”), or a coccidia strain derived from master seed and not directly used for manufacturing the products (hereafter referred to as “working seed coccidia”).

“Production seed” is a virus strain derived from the working seed and directly used for manufacturing the products (hereafter referred to as “production seed virus”), a bacteria strain derived from working seed and directly used for manufacturing the products (hereafter referred to as “production seed bacteria”), or a coccidia strain derived from working seed and directly used for manufacturing the products (hereafter referred to as “production seed coccidia”).

21 “Cell line” indicates cultured cells having the continuous propagation ability and used for manufacturing seed lot products.

“Master cell seed” indicates cultured cells that have been passaged not more than approved passages.

“Working cell seed” indicates a cell line derived from the master cell seed and not directly used for manufacturing the products.

“Production cell seed” is a cell line derived from the working cell seed and directly used for manufacturing the products.

22 “Master primary cell seed” indicates primary cultured cells generated through not more than five passages of cells that have been collected from animals.

“Working primary cell seed” indicates primary cultured cells derived from the master primary cell seed and not directly used for manufacturing the products.

“Production primary cell seed” is primary cultured cells derived from the working primary cell seed and directly used for manufacturing the products.

23 “Bulk material” indicates a veterinary biological product containing a single active ingredient that is not dispensed as is into final containers.

24 “Final bulk” indicates a bulk drug prepared in one vessel and ready for immediate filling into final containers. The content shall be completely homogeneous in terms of pharmaceutical properties and qualities. Shaking is allowed to maintain homogeneity.

25 “Final product” indicates the products filled into small containers from a final bulk, freeze-dried if necessary, and hermetically sealed.

26 “Lot” usually indicates a group of final products derived from the final bulk. Also, the “lot” of bulk material or final bulk in the monograph of drugs that serves as veterinary biological products indicates a group of products having a uniform character and quality that has been filled in a series of manufacturing processes within a specified period.

27 In general, the same manufacturing number or manufacturing code is assigned to the products of one lot. However, additional numbers or marks shall be assigned to the individual final lots or freeze-dried lots, if dispensed and hermetically sealed under different operating conditions (the amount to be dispensed may vary) or if freeze-dried under different drying conditions, respectively.

28 Generally, tests on specifications for bulk material or final bulk and final lot products required in the monographs are collectively performed with samples from the same lot. For final products having individual final lots or individual freeze-dried lots, however, the following tests shall be conducted on individual lots: properties test, sterility test, viable count test, spore count test, test for freedom from contaminant microorganisms, test for virus content, vacuum degree test, test for moisture content, and additionally specified tests. Other tests shall be conducted by taking and mixing equal volumes of the test sample of individual lots.

29 “Test for freedom from abnormal toxicity,” “Toxicity limit test,” “Safety test,” and “Potency test” for final lot products specified in the monographs may be omitted when the requirements otherwise specified by the Director of the National Veterinary Assay Laboratory are met.

30 “Test sample” indicates a final product used for tests or the final product dissolved with diluent.

“Test article” indicates a product subject to tests on the final bulk or earlier stages that has not been manipulated in any way.

“Test material” indicates a test sample or article that has been diluted or otherwise manipulated.

31 Generally, tests on veterinary biological products freeze-dried or intended to be dissolved drug for use in the monographs, unless these tests are the “Vacuum degree test,” “Test for moisture content,” “uniformity test per container of freeze-dried product before dissolution” in the “Properties test,” and otherwise specified, shall be conducted on solutions diluted or suspended according to the method stated on the container using the diluents.

32 The “Inactivation test” evaluates the loss or reduction in biological activity of viable microorganisms used in the production of a veterinary biological product below the level specified in the requirements.

The “Detoxication test” evaluates the loss of toxicity of toxic substances present during the production process of a veterinary biological product below the level specified in the requirements.

The “Test for freedom from (name of microorganism or substance)” determines the absence of substances or microorganisms indicated in ( ) below the level specified in the requirements.

33 Unless otherwise specified, tests shall be conducted at room temperature.

Room temperature is defined as 15℃ to 25℃.

34 Unless otherwise specified, tests shall be conducted in accordance with the “Reagents, Test Solutions, Etc.” of the General Tests.

The term “water” for use in the tests indicates purified water specified by the JP.

35 To “accurately weigh” means weighing to the specified digit.

To “exactly measure” means measuring the specified whole volume using pipettes, measuring flasks, or burettes.

To “precisely weigh” means weighing to the lowest digit, for example, 0.1 mg, 0.01 mg, or 0.001 mg.

36 Numerical values shall indicate the specified value with a ± 5% variation.

“Approximately” in collecting the desired amount or quantity indicates a variation in numerical value within ±10%.

37 When a test result is judged by comparing a specified value (hereafter referred to as “specified value”) with actually measured values obtained from a test (hereafter referred to as “experimental values”) in the Physiochemical Test of the General Tests, experimental values shall be obtained to one digit lower than that for the specified value and rounded off to the same digit with the specified value.

38 Animals used in tests must be healthy. If animals exhibit incidental abnormalities during the test, the veterinary biological product shall not meet the test requirements unless the abnormalities can be demonstrated to be unrelated to the product tested.

39 The test methods or the details of the test methods specified in the Minimum Requirement for Veterinary Biological Products may be changed so far as it is equally or more precise and accurate than the specified method. However, if the test results are different from the ones by using the specified method of the Minimum Requirements for Veterinary Biological Products, the final judgement of the test shall be made in accordance with said specified method.

40 Unless otherwise specified, storage temperature shall be kept ≤ 10℃ for freeze-dried products and 2℃ to 10℃ for liquid products in a light-shielded environment. However, this shall not apply to bulk material or final bulk.

41 “Delivery from the warehouse” means the shipping of the veterinary biological products from the storage of the manufacturing facility for sales or transport. Veterinary biological products shall be stored at a constant temperature before shipping

42 Unless otherwise specified, the shelf life and expiry date shall be set based on the month following the month of the day when production is completed. However, for veterinary biological products to be subjected to national certification tests according to Article 43 (1) of the Law, the date when the national certification test is completed may be substituted for the date when production is completed.

43 In cases where veterinary biological products should be subject to the national certification test but could not be submitted for application within the period specified in Article 152, Section 3, of the Regulatory Rules for Veterinary Medicinal Products (Ordinance of the Ministry of Agriculture, Forestry and Fisheries No. 107, 2004) under unavoidable circumstance when Director of National Veterinary Assay Laboratory determines that particularly there is any reason for shortening the expiry date as the result of the national certification test, the shelf life of such products shall be defined as the date specified by the director notwithstanding above provisions.

44 Unless specified otherwise, entries on the immediate container for monographs required by Article 50 (9) of the Law shall be those listed below.

(1) Storage conditions

(2) Expiry date

(3) Live or inactivated for vaccines

However, these entries may be omitted when they are provided on the outer container or package if the following conditions apply:

-The product is provided in an ampoule or direct container or package with a volume of 2 mL or less.

-The product is provided in an ampoule or container with a volume of more than 2 mL having an area on which these entries are directly printed but less than 10 mL having an area insufficient to clearly label the entries specified in the provisions of Article 50 of the Law.

-The product is designed for in vitro diagnostic purposes and provided in the outer container or package stating “For in vitro diagnostic purposes.”

45 When the monographs or pharmaceuticals used for the production of the monographs are derived from animals, these animals must be healthy, unless otherwise specified.