

Outline of Regulation System of Veterinary Drugs in Japan

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1. Organization and functions of veterinary pharmaceutical administration

The Ministry of Agriculture, Forestry and Fisheries (MAFF) controls veterinary drugs (drugs exclusively used for animals), and the Ministry of Health, Labor and Welfare (MHLW) controls drugs for human use.

1) Responsible office for veterinary drugs;

Animal Products Safety Division (APSD), Food Safety and Consumer Affairs Bureau,
Ministry of Agriculture, Forestry and Fisheries (MAFF)

- Regulation for veterinary drugs (approval, license, examination, inspection, guidance, etc.) of veterinary drugs

2) Facility for veterinary drugs;

National Veterinary Assay Laboratory (NVAL), MAFF

- National assay, testing, study for reliability standard compliance, inspection and guidance of veterinary drugs

3) Council for veterinary drugs;

Pharmaceutical Affairs Sub-council, Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

- Investigation of veterinary drugs; (i.e. approval of new drugs, reexamination or reevaluation of approved drugs)

- Establishment of standards for veterinary drugs †

4) Related organization of veterinary drugs

a. Fish and Fishery Products Safety Office, APSD, Food Safety and Consumer Affairs Bureau, MAFF

- Examination of drugs for fishery use etc.

b. Animal Health Division, Food Safety and Consumer Affairs Bureau, MAFF

- Regulation for livestock animal infectious diseases

c. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW

- Services concerning the Japanese Pharmacopoeia including veterinary drugs

d. Standard and Evaluation Division, and Inspection and Safety Division, Department of Food Safety, Pharmaceutical and Food Safety Bureau, MHLW

- Regulation concerning residue of agricultural chemicals, drugs etc. in foods

e. Food Safety Commission, Cabinet Office

- Assessment of the effect of food on health (Risk assessment of food in relation to veterinary drugs)

2. The pharmaceutical affairs law (Law No. 145 Series of 1960)

Veterinary drugs are controlled directly by the Pharmaceutical Affairs Law and

relevant regulations. The purpose of the Law is to regulate matters pertaining to drugs, quasi-drugs, cosmetics and medical devices so as to ensure their quality, efficacy and safety at each stage of development, manufacturing (importing), marketing, retailing and usage.

The outline of the Pharmaceutical Affairs Law related to veterinary drugs is described as follows.

- 1) Veterinary drugs are under the control of the MAFF. In this law, as far as drugs, which are intended for exclusive use with animals, "the Minister of Health, Labor and Welfare" shall be replaced as "the Minister of Agriculture, Forestry and Fisheries; "MHLW ordinance" shall be replaced as "MAFF ordinance". (Article 83)
- 2) A person intending to market release of veterinary drugs shall obtain the license for marketing approval holders (Article 12) and the marketing approval for each drug (Article 14). The Minister of Agriculture, Forestry and Fisheries (the Minister) issues the license and approval.
- 3) Without the license for manufacturing veterinary drugs, no one shall engage in business to manufacture veterinary drugs. The license shall be granted by the Minister for each manufacturing facilities, according to the category specified by MAFF ordinance. (Article 13)
- 4) A person intending to manufacture veterinary drugs in foreign countries, which will be imported to Japan from overseas may be accredited by the Minister as a foreign manufacturer. The accreditation shall be granted for each manufacturing facilities according to the category specified by MAFF ordinance. (Article 13-3)
- 5) A person obtaining the marketing approval of new veterinary drugs shall apply for the reexamination of such drugs after six years from the new approval (Article 14-4). Other drugs, that already approved, shall apply for reevaluation based on designation of the Minister. (Article 14-6)
- 6) A person who manufactures active pharmaceutical ingredients of veterinary drugs may register the name, ingredients, manufacturing methods, properties, quality or storage of the active pharmaceutical ingredient in a drug master file. (Article 14-11)
- 7) Any person intending to establish a pharmacy or to retail drugs shall obtain a license from the governor of the prefecture where his/her office is located. (Article 4 and 24)
- 8) The Japanese Pharmacopoeia and other relevant standards are established based on the law. (Article 41 and 42)
- 9) Distribution of drugs with poor quality, improperly labeled, unapproved, not yet performed national assay as well as extravagant advertising shall be prohibited. (Article 55, 56 and 66)
- 10) Proper supply of drugs is secured by means of national assay, spot inspections, national test etc. (Article 43, 69, 71 etc.)
- 11) No proprietor of a pharmacy and no retailer of drugs shall retail drugs so designated by the Minister to persons other than those who have received a prescription or direction from a veterinarian. (Article 49)
- 12) No person shall provide unapproved veterinary drugs which will be provided animals for food production. (Article 83-3)
- 13) The Minister shall be able to enact restriction on the use of drugs which will be provided animals for food production. (Article 83- 4 , 83-5)

Regulations of veterinary drugs under the Law from the stage of their development to post-marketing evaluation are shown in Fig. 1.

3. License for marketing approval holders of veterinary drugs

1) Procedure of application for license

A person intending to market release of veterinary drugs, (excluding drugs being active ingredients) who has manufactured (including manufacturing entrusted to another person, but not including manufacturing entrusted from another person) or imported, shall obtain the license for marketing approval holders of veterinary drugs. The MAFF examines an application, on the basis of data submitted by the applicant, and the Minister grants the license specified in the right column of the following table according to the classification of drugs specified in the left column of the table. The license shall be renewed every 5 years.

Classification of drugs	Types of licenses
Drugs designated as drugs requiring prescription or direction of veterinarian by the Minister pursuant to the provisions of Article 49, Paragraph 1	No. 1 type of license for marketing approval holder of veterinary drugs
Drugs other than those complying with the preceding paragraph	No. 2 type of license for marketing approval holder of veterinary drugs

2) Standards for License

The applicant shall comply with the standards of a method of quality control of veterinary drugs (Good Quality Practice. the Ministerial ordinance No. 19, 2005) and the standards of a method of post-marketing safety management of veterinary drugs (Good Vigilance Practice. the Ministerial ordinance No. 20, 2005) to obtain the license for marketing approval.

4. Marketing approval of veterinary drugs

1) Procedure for marketing approval

Before granting the approval, the MAFF examines each product by name, ingredient and its composition, manufacturing methods, administration and dosage, indications or effects, and adverse reactions etc., on the basis of data submitted by the applicant. The NVAL cooperates with the APSD to examine applications for approval. Approval of a drug guarantees quality, efficacy and safety claimed.

The Minister grants the marketing approval on the presupposition that the approved drug shall be manufactured by the licensed manufacturer or the accredited foreign manufacturer.

An application for approval of a new veterinary drugs first undergoes an investigation by a subcommittee of the Pharmaceutical Affairs Sub-council (PASC) specialized in the category of the drug applied. Further a drug for food producing animals is investigated a matter of residue of drugs by the subcommittee on residue problem of veterinary drugs. Additionally, the application is subjected to an examination by the committee on veterinary drugs of the PASC and then by the executive committee of the PASC.

Furthermore, veterinary drugs which are provided as food shall be assessed the safety to human health by the Food Safety Commission, Cabinet Office.

After the examination and the assessment, the Minister grants the marketing approval

of veterinary drugs to applicant.

The standard periods for grant procedure, from the day the Minister receives the approval application until the Minister grants the marketing approval for the drug, is within 12 months. However, this period does not include duration for preparation of additional information required by the review committee of the PASC or for correction of inadequacies in the approval application, and duration for submission of additional documents.

Additionally, the Minister enacts following three standards of drugs that based on the provisions of Article 42 of the Pharmaceutical Affairs Law.

- a. Minimum requirements for veterinary biological products (Notice No. 1567, 2002)
- b. Standard of antibiotics for animals (Notice No.1123, 1999)
- c. The source materials standards of biological products for animal use (Notice No. 1911, 2003)

The NVAL prepares each draft of the standard of veterinary drugs.

Drugs regulated on the standard shall be conformed to the standard.

2) Data required for applications and standards for trust of data

An application for approval is examined on the basis of data submitted by an applicant. The data required for approval is determined by the conditions of a drug whether the drug contains a new active ingredient or not. Category of data required and class of drugs are specified in Table 1 or Table 2.

Fundamental guidelines for applicants to make up a set of test data and studies, which is necessary to be attached to the application, is established.

Additionally, data of toxicity, target animal safety or residue has to meet the Ministerial ordinance (No. 74, 1997) of the Good Laboratory Practice (GLP), and data of clinical trial has to meet the Ministerial ordinance (No. 75, 1997) of the Good Clinical Practice (GCP). Staffs of the NVAL inspect laboratories and clinical trial institutions in a part of examination for approval.

Furthermore, the drug (include active pharmaceutical ingredient) in the application shall be confirmed that the method of manufacturing control or quality control of it in the manufacturing establishment complies with the standard for GMP software specified by the Ministerial Ordinance (No. 18, 1994). Compliance of the standard is checked by staff of the MAFF, and they reviews the application through documents or inspection or on site inspection. The confirmation shall be renewed every 5 years.

5. Drug master file for animals

A person who manufactures active pharmaceutical ingredients etc. (including those who manufacture in foreign countries) may register in a drug master file that specified by the Ministerial ordinance (No. 107, 2004). It is including the name, ingredients, manufacturing methods, properties, quality or storage of the active pharmaceutical ingredient etc.

When the Minister has registered active pharmaceutical ingredients etc., the Minister shall publish the registration number and date, the name/address of the trader and the name of the article.

Further when a drug contained the registered ingredient is applied for the marketing approval, it is possible to omit a part of document to submit.

6. License for manufacturer of veterinary drugs

1) Classification of license and standards for license

Anyone who intends to manufacture drugs in business has to obtain manufacturing license. The license guarantees quality of facilities in which a drug is manufactured, tested or stored.

The license shall be granted by the Minister for each manufacturing facilities as the following table.

Classification	Type of drug and contents of manufacturing process
1	All or a part of manufacturing process of the following drugs a. Biological products (excluding <i>in vitro</i> diagnostic reagents) b. Drugs targeted national assay (excluding classification 1-a and 3) c. Drugs applied gene recombination technology (excluding classification 3), etc.
2	All or a part of manufacturing process (excluding classification 5) of aseptic drugs (excluding classification 1 and 3)
3	All or a part of manufacturing process (excluding classification 5) of <i>in vitro</i> diagnostic reagents
4	All or a part of manufacturing process (excluding classification 1, 2 and 3) of drugs (excluding classification 5)
5	Factory for packaging, labeling or storage of drugs (excluding Classification 1)

Each factory shall conform to the ministerial ordinance (No. 35, 2005) of structure and facilities of the factory (GMP hardware) to obtain the license. The license shall be renewed every 5 years. A pharmaceutical inspector of national/prefecture government inspects the factory before renewal of the license.

7. Accreditation of foreign manufacturers veterinary drugs

A person intending to manufacture veterinary drugs in foreign countries to export to Japan may be accredited by the Minister as a foreign manufacturer. The Minister grants the accreditation for each manufacturing factory as the same classification in the case of manufacturing license mentioned above.

The accreditation shall be renewed every 5 years.

8. Retailing Control of Veterinary drugs

1) License for retailing drugs

Anyone shall not retail veterinary drugs without a license for retailing of veterinary drugs, or without a license for pharmacy. The governor of 47 prefectures in Japan grant the license for a pharmacy or a retailer of veterinary drugs, and the license shall be renewed every 6 years.

2) Pharmaceutical inspection

Approximately 2,000 veterinary pharmaceutical inspectors are stationed through nation, including the national government, to inspect marketing approval holders,

manufacturers, and retailers of veterinary drugs. Veterinary pharmaceutical inspectors are government officials belonging to the livestock hygiene service center, etc. of each prefecture.

The veterinary pharmaceutical inspectors regularly make on site inspection of drug marketing approval holders, manufacturers and drug retailers etc. Their major duties are as follows.

- a. For on site inspection of compliance with GQP, GVP and GMP hardware
- b. To observe unapproved drugs, unlicensed drugs, defective drugs, and drugs with illegal labeling
- c. To control false, exaggerated advertisement and non-licensed retailer.

9. National assay and national test of veterinary drugs

1) National assay of biological products

The drugs designated by the Minister shall be assayed by the person designated by the Minister. The Minister designates biological products (vaccines, sera and diagnostic reagents for infectious disease) which require advanced manufacturing techniques and testing methods as objects of the national assay. The Minister designates the NVAL as an official assay institution in the Ministerial ordinance (No. 107, 2004).

The assay is performed on each lot/batch of products, according to the provisions of the Ministerial notice (No.1568, 2002) before marketing. Rejected products by the assay are discarded in the presence of a pharmaceutical inspector.

2) National test of antibiotics etc.

Newly approved antibiotics or screening drug for blood type diagnostics shall be tested for every 30 lots of product or during 2 years on the basis of the Minister's order at the NVAL. Rejected products by the test are discarded.

3) Spot sampling test

To remove harmful drugs in the process of manufacturing and marketing, and to ensure quality, NVAL performs quality test of veterinary drugs sampled by pharmaceutical inspectors at factories or in market. Disqualified drugs by the test are recalled and discarded.

10. Proper application of veterinary drugs

1) Drugs requiring directions or prescription

The Minister designates certain drugs which need special consideration and attention by the drug users as drugs requiring directions or prescriptions of a veterinarian at the time of sale. Antibiotics, hormones, vaccines, etc. for cattle, horse, sheep, goat, pig, dog, cat and chicken classified to this category.

2) Prohibition of application of unapproved drug

Any person shall not provide unapproved drugs to the live stock animals (cattle, pigs or other animals specified by the MAFF ordinance, which are provided as food). This provision shall not apply when veterinary drugs are intended to use for research and development, or in case it is specified by the MAFF ordinance (No. 70, 2003).

3) Restriction on use of veterinary drugs

The Minister enacts the standard (the MAFF ordinance No. 42, 1980) on drug usage, to assure the public health safety in administration of anti microbial preparations, etc. to food producing animals, such as meat or milk-producing animals, poultry, fish or bees. This standard includes requirements to specify drugs that can be used, and its administration,

dosages, and prohibition periods for use to subject animals.

The NVAL performs studies on confirmation of prohibition period to reexamine the period.

4) Drugs requiring veterinary consultation

Any veterinarian shall not provide or prescribe poisonous and powerful drugs, biological products, drugs requiring directions or prescription, and drugs regulated on the use for animals without consultation of herself/himself. (The Veterinary Act (Law No. 186 Series of 1949), Article 18)

11. Post-marketing surveillance of veterinary drugs

1) Reexamination of new drugs

Data of new drugs, that submitted for marketing approval, is not always adequate. Main reason is due to the fact that the drug has been tested only under controlled conditions or tested for limited cases. On the other hand, there may be useful information of new drugs in practical use under various conditions, that can be fed back to drug administration. Therefore, reexamination system has been established to review the efficacy and safety of a new drug, on the basis of results of field investigations that conducted by marketing approval holders within six years after the drug's approval.

The MAFF performs the reexamination with the results of application of the drug, spontaneous drug reaction, investigations of situations of the drug in foreign countries, and literature surveys conducted by the marketing approval holder of the drug.

The data concerned the reexamination has to be collected and compiled in accordance with the Ministerial ordinance (No. 33, 2005) of the Good Post-marketing Study Practice (GPSP). Staffs of the NVAL inspect conformity to GPSP of the data.

2) Reevaluation of drugs

When quality, efficacy or safety of a drug is suspected with level of recent veterinary and pharmaceutical sciences, the drug must be reevaluate in accordance with the announcement of the Minister. The data for reevaluation has to be collected and compiled in accordance with GPSP also.

Staffs of the NVAL collect and arrange scientific information related to quality, efficacy and safety of veterinary drugs. The results are applied to select drugs for reevaluation on the examination by the PAFSC.

REFERENCE

- 1 Pharmaceutical Review System Study Group, Ministry of Health and Welfare, Pharmaceutical Administration In Japan. -8th Edition-(In Japanese & English), Yakuji Nippo, LTD, (1998)
- 2 The Japanese Federation of Medical Devices Associations, The Pharmaceutical Affairs Law - New Regulations Effective in 2005 - (Bilingual in Japanese and English), Yakuji Nippo, LTD, (2004)

Table 1. Data Required for the Application of Approval of Veterinary Pharmaceutical Products.

Category and type of data	Class of drugs for application*					
	(1)	(2)	(3)	(4)	(5)	(6)
A. Origin or discovery of drug, condition of use in foreign countries, etc.						×
B. Data on physical and chemical properties (e.g. data on determination of structure, data on physical and chemical properties, data on specification and test methods, etc.)						
C. Data on production						
D. Data on stability (e.g. data on long-term storage test, data on severe test, data on acceleration test, etc.)						
E. Data on toxicity 1. Data on acute toxicity 2. Data on sub acute and chronic toxicity 3. Data on special toxicity (e.g. mutagenicity, local irritation, etc.)			×		×	×
			×		×	×
			×	×	×	×
F. Data on safety for target animal						
G. Data on pharmacological action 1. Data on effectiveness 2. Data on general pharmacology						×
		×	×		×	×
H. Data on absorption, distribution, metabolism and Excretion						
I. Data on results of clinical trials						×
J. Data on residue study						

* Class of drugs for application

(1) Drugs containing a new active ingredient

(2) Drugs in new route of administration

(3) Drugs in new dosage and providing a new indication

(4) New combination drugs

(5) Combination drugs in new dosage and providing a new indication

(6) Drugs in similar formulation of drugs already approved

: Data shall be submitted.

× : Data may be omitted.

: Data submission shall be determined depending upon the conditions of drugs.

Table 2. Data Required for the Application for Approval of Veterinary Biological Products

Category and type of data	Class of drugs for application*						
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
A. Data on origin, details of discovery, use in foreign countries, etc.							×
B. Data on physical and chemical properties, etc. (e.g. data on preparation of seed, data on physicochemical and biological properties, data on specification and test methods, etc.)							
C. Data on production							
C. Data on stability (e.g. data on long-term storage test, data on stability at usage condition, etc.)							
E. Data on safety for target animal						×	×
F. Data on pharmacological action (e.g. data on effectiveness, data on time for immunization and the duration, etc.)						×	×
G. Data on results of clinical trials					×	×	×

* Class of drugs for application

(1) Drugs containing a new active ingredient or a new combination prescription drugs

(2) Drugs in new composition of the approved ingredient

(3) Drugs in new route of administration

(4) Drugs providing a new indication

(5) Drugs in new dosage

(6) Though a seed for production is different, the property of the seed is judged to be equivalent to

those of the approved one at the National Veterinary Assay Laboratory.

(7) Drugs in similar formulation of drugs already approved

: Data shall be submitted.

× : Data may be omitted.

: Data submission shall be determined depending upon the conditions of drugs.

Fig.1 Regulation of Veterinary Drugs from Development to Post-marketing Stage

