Outline of Regulation System of Veterinary Medicinal Products (VMPs) in Japan
—To ensure quality, efficacy and safety of VMPs based on the Pharmaceutical Affairs Law—

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADI</td>
<td>Acceptable Daily Intake</td>
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<tr>
<td>APSD</td>
<td>Animal Products Safety Division</td>
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<td>FSCAB</td>
<td>Food Safety and Consumer Affairs Bureau</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>GPS</td>
<td>Good Post-marketing Study Practice</td>
</tr>
<tr>
<td>GQP</td>
<td>Good Quality Practice</td>
</tr>
<tr>
<td>GVP</td>
<td>Good Vigilance Practice</td>
</tr>
<tr>
<td>LMOs</td>
<td>Living Modified Organisms</td>
</tr>
<tr>
<td>MAFF</td>
<td>Ministry of Agriculture, Forestry and Fisheries</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorization Holder</td>
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<tr>
<td>MHLW</td>
<td>Ministry of Health, Labor and Welfare</td>
</tr>
<tr>
<td>Minister</td>
<td>Minister of Agriculture, Forestry and Fisheries</td>
</tr>
<tr>
<td>MRL</td>
<td>Maximum Residue Limit</td>
</tr>
<tr>
<td>NVAL</td>
<td>National Veterinary Assay Laboratory</td>
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<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
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<td>OIE</td>
<td>International Epizootic Office: World Organization for Animal Health</td>
</tr>
<tr>
<td>PAFSC</td>
<td>Pharmaceutical Affairs and Food Sanitation Council</td>
</tr>
<tr>
<td>PASC</td>
<td>Pharmaceutical Affairs Sub-council,</td>
</tr>
<tr>
<td>VICH</td>
<td>International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products</td>
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<tr>
<td>VMPs</td>
<td>Veterinary Medicinal Products (Drugs for animal use)</td>
</tr>
</tbody>
</table>
1. Organization and Functions of Veterinary Pharmaceutical Administration

The Ministry of Agriculture, Forestry and Fisheries (MAFF) controls veterinary medicinal products (VMPs) exclusively used for animals under the Pharmaceutical Affairs Law (Law No. 145, Series of 1960). The Ministry of Health, Labor and Welfare (MHLW) controls pharmaceuticals for human use.

National administrative authorities and their functions for VMPs are as follows.

1) Animal Products Safety Division (APSD), Food Safety and Consumer Affairs Bureau (FSCAB), Ministry of Agriculture, Forestry and Fisheries (MAFF): Legislative authority for VMPs
   - Planning of regulation and administration for risk management of VMPs
   - Management of marketing approval
   - Licensing of marketing authorization holder (MAH), manufacturer
   - Accreditation of foreign manufactures
   - Pharmaceutical supervision, guidance, etc.

2) Fish and Fishery Products Safety Office, APSD, FSCAB, MAFF
   - Examination of VMPs for fishery use
   - Guidance for proper application of VMPs for fishery use

3) National Veterinary Assay Laboratory (NVAL), MAFF: Technical service for VMPs
   - Examination of application for marketing approval, reexamination and reevaluation
   - GMP inspection
   - GLP/GCP inspection
   - National assay and testing
   - Distribution of standard materials for test
   - Technical guidance
   - Research for regulatory science
   - International technical cooperation (action for OIE collaborating center, action for expert working groups of VICH, etc.)

4) Committee on Veterinary Products, PASC, PAFSC: Council for VMPs
   - Investigation important items for VMPs. For example,
     - Approval of new VMPs,
     - Reexamination or reevaluation of approved VMPs
     - Establishment of standards for VMPs
     - Establishment of withdrawal period of VMPs for food producing animal use

5) Other authorities related of VMPs
   a. Animal Health Division, FSCAB, MAFF
      Control and prevention of animal diseases
   b. Plant products Safety Division
      - Regulation on the use of living modified organisms (LMOs) for VMPs
   c. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW
2. Outline of the Pharmaceutical Affairs Law to ensure quality, efficacy and safety of VMPs

VMPs are controlled directly by the Pharmaceutical Affairs Law, the Pharmaceutical Affairs Law Enforcement Ordinance (Government Ordinance No. 11, Series of 1961), The Control Regulations of Veterinary Medical Products (MAFF Ministerial Ordinance No.107, Series of 2004), etc.

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

1) Alternative reading for VMPs
   - In this law, as far as drugs, which are intended for exclusive use with animals (VMPs), "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) Objectives
   - This law is intended to provide regulations required to ensure the quality, efficacy and safety of drugs, quasi-drugs, cosmetics (out of scopes for animal use) and medical devices and to improve the public health and hygiene.

3) License for Marketing Approval Holder or Manufacturer, Marketing Approval, etc.
   - A person intending to market release of a VMP shall obtain the license for MAH. The Minister of Agriculture, Forestry and Fisheries (the Minister) issues the license and approval. (Article 12)
   - Without the license for manufacturing VMPs, no one shall engage in business to manufacture VMPs. The license shall be granted by the Minister for each manufacturing facilities, according to the category specified by MAFF ordinance. (Article 13)
   - A person intending to manufacture an overseas VMP which will be imported to Japan from the country 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)
   - A person intending to market each VMP shall be obtained formal approval from the Minister. (Article 14)
   - A person obtaining the marketing approval of a new VMP shall apply for the reexamination of such product after six years from the new approval (Article 14-4). Other VMPs, that already approved, shall apply for reevaluation based on designation of the Minister. (Article 14-6)
   - A person who manufactures active pharmaceutical ingredients of VMPs may register the
name, ingredients, manufacturing methods, properties, quality or storage of the active pharmaceutical ingredient in a drug master file. (Article 14-11)

4) Pharmacy or Retailing Business
   ✷ Any person intending to establish a pharmacy or to retail VMPs shall obtain a license from the governor of the prefecture where his or her office is located. (Article 4 and 24)

5) Standards and Tests
   ✷ The MHLW shall establish and publish the Japanese Pharmacopoeia (Article 41)
   ✷ The Minister may establish the standard of VMPs. (Article 42)

6) Handling, Advertising, Supervision, etc.
   ✷ Distribution of VMPs with poor quality, improperly labeled, unapproved, not yet performed national assay as well as extravagant advertising shall be prohibited. (Article 55, 56 and 66)
   ✷ Proper supply of VMPs are secured by means of national assay, spot inspections, national test etc. (Article 43, 69, 71 etc.)
   ✷ No proprietor of a pharmacy and no retailer of VMPs shall retail VMPs so designated by the Minister to persons other than those who have received a prescription or direction from a veterinarian. (Article 49)

7) Report of adverse reactions
   When marketing authorization holders of VMPs are informed of any adverse reaction, etc. as specified by MAFF ordinance for their marketed products, they must report it to the Minister. (Article 77-4-2)

8) Handling of Clinical Trials
   ✷ Provisions concerning clinical trials are enacted, including requirements for the sponsor of clinical trials.

9) Handling of VMPs
   ✷ Prohibition of Manufacturing and Import of VMPs without license: No person shall manufacture VMPs without license of a manufacturer, and import VMPs without license for a marketing approval holder in principle. (Article 83-2)
   ✷ Prohibition of Use of unapproved VMPs: No person shall provide unapproved VMPs which will be provided animals for food production in principle. (Article 83-3)
   ✷ Restriction on Use of VMPs: The Minister shall be able to enact restriction on the use of VMPs which will be provided food producing animals. (Article 83-4, 83-5)

Regulations of VMPs under the Law from the stage of their development to post-marketing evaluation are shown in Fig. 1.
Fig. 1 Regulation of Veterinary Medicinal Products (VMPs) in Japan

I. Examination for Marketing Approval
- Marketing approval
  - GLP, GCP, GMP
- Drug master file
- Pharmacopoeia
  - National Standards

II. Marketing Authorization Holder, Manufacturing and Quality Control
- License for marketing authorization holder
  - GQP & GVP
- License for manufacturer
  - GMP (structure & facility)
- Accreditation for foreign manufacturer
  - GMP (structure & facility)

III. Distribution Control
- License for pharmacy or retailing VMPs
- Regulations for management, buildings and facilities
- Prescription of direction for retailing of vaccine, antibiotics, etc.
- Regulation for use of VMPs to food producing animals

IV. Evaluation Control
- Reevaluation GPSP
- Reexamination GPSP
- Report of adverse reactions

< GXP: Ministerial ordinance >
GLP: Good Laboratory Practice
GCP: Good Clinical Practice
GMP: Good Manufacturing Practice
GMP (structure & facility): Regulation of GMP hardware
GQP: Good Quality Practice
GVP: Good Vigilance Practice
GPSP: Good Post-marketing Study Practice
3. License System for MAH

1) Procedure of application for license

A person intending to market release of VMPs (excluding products 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 MAH of VMPs. 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 VMPs specified in the left column of the table. The license shall be renewed every 5 years.

<table>
<thead>
<tr>
<th>Classification of VMPs</th>
<th>Type of license</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products designated as VMPs requiring prescription or direction of veterinarian by the Minister pursuant to the provisions of Article 49, Paragraph 1</td>
<td>No. 1 type of license for MAH of VMPs</td>
</tr>
<tr>
<td>VMPs other than those complying with the preceding paragraph</td>
<td>No. 2 type of license for MAH of VMPs</td>
</tr>
</tbody>
</table>

2) Prerequisite standards for license of MAH

The MAH shall be responsible for handling VMPs. The applicant shall comply with the standards of a method of quality control of VMPs (GQP: the Ministerial ordinance No. 19, Series of 2005) and the standards of a method of post-marketing safety management of VMPs (GVP: the Ministerial ordinance No. 20, Series of 2005) to obtain the license for marketing approval.

4. License System for Manufacturer

1) Classification of license

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

The license shall be granted by the Minister for each manufacturing facilities as the following table 2. The license shall be renewed every 5 years.
Table 2. Classification of license for manufacturer of VMPs

<table>
<thead>
<tr>
<th>Classification of manufacturer</th>
<th>Type of VMPs and contents of manufacturing process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All or a part of manufacturing process of the following products a. Biological products (excluding <em>in vitro</em> diagnostic reagents) b. VMPs targeted national assay (excluding classification 1-a and 3) c. VMPs applied gene recombination technology (excluding classification 3), etc.</td>
</tr>
<tr>
<td>2</td>
<td>All or a part of manufacturing process (excluding classification 5) of aseptic VMPs (excluding classification 1 and 3)</td>
</tr>
<tr>
<td>3</td>
<td>All or a part of manufacturing process (excluding classification 5) of <em>in vitro</em> diagnostic reagents</td>
</tr>
<tr>
<td>4</td>
<td>All or a part of manufacturing process (excluding classification 1, 2 and 3) of VMPs (excluding classification 5)</td>
</tr>
<tr>
<td>5</td>
<td>Factory for packaging, labeling or storage of VMPs (excluding Classification 1)</td>
</tr>
</tbody>
</table>

2) Prerequisite standard for license of manufacture

Each factory shall conform to the ministerial ordinance (No. 35, Series of 2005) of structure and facilities of the factory (GMP for VMPs related to the Structure and Facilities) to obtain the license. A pharmaceutical inspector of national or prefecture government inspects the factory before renewal of the license.

5. Accreditation System of Foreign Manufacturers

A person intending to manufacture VMPs 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.

Each factory shall conform to the ministerial ordinance of GMP for VMPs related to the Structure and Facilities to obtain the accreditation.

The accreditation shall be renewed every 5 years.

6. Marketing Approval System

1) Procedure for marketing approval

Before granting the approval, the MAFF examines each VMP 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 performs examination and evaluation of applications for approval. Approval of a VMP guarantees quality, efficacy and safety claimed.

The Minister grants the marketing approval on the presupposition that the approved VMP shall be manufactured by the licensed manufacturer or the accredited foreign manufacturer.
An application for approval of a new VMP undergoes first an investigation by each Sub-committee (i.e. Biological Products, Antimicrobial Products, General Medicaments or Fisheries Products) of the Committee on Veterinary Products of the PASC specialized in the category of VMPs. Further a VMP for food producing animals is investigated a matter of residue of the product by the Sub-committee on residue problem of VMPs. Additionally, the application is subjected to an examination by the Committee on Veterinary Products of the PASC and then by the executive committee of the PASC.

By the way, The Minister of Health, Labor and Welfare establishes Maximum Residue Limit (MRL) of VMPs in foods based on the Food Sanitation Act (Law No. 233, Series of 1947).

Furthermore, VMPs which are provided as food shall be assessed the safety to human health by the Food Safety Commission, Cabinet Office. This Commission establishes acceptable daily intake (ADI) of each ingredient of VMPs.

After the examination and the assessment, the Minister grants the marketing approval of VMPs 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 VMP, 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.

2) Minimum requirements (Standard for VMPs)

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

a. Minimum requirements for veterinary biological products (Notice No. 1567, Series of 2002)

b. Standard of antibiotics for animals (Notice No.1123, Series of 1999)

c. Standards for veterinary biological materials (Notice No. 1911, Series of 2003)

These products designated to the standard shall be conformed to each standard.

The NVAL prepares each draft for revision of the standard of VMPs.

3) Data required for applications

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 VMP whether the VMP contains a new active ingredient or not. Category of data required and class of VMPs are specified in Table 1 and Table 2. And examples of contents of data for application are attached as Appendix 1 and Appendix 2.

Fundamental guidelines for applicants to make up a set of test data are established.

By the way, VICH (International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products) has been in action as a trilateral (EU-Japan-USA) program aimed at harmonizing technical requirements for VMPs registration from 1996. The VICH develops many guidelines on quality, safety, efficacy, etc..
Table 3. Data Required for the Application of Approval of Veterinary Medicinal Products (VMPs)
Except Biological Products.

<table>
<thead>
<tr>
<th>Category and type of data*</th>
<th>Class of VMPs for application**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>A. Origin or discovery of drug, condition of use in foreign countries, etc.</td>
<td>○</td>
</tr>
<tr>
<td>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 method, etc.)</td>
<td>○</td>
</tr>
<tr>
<td>C. Data on production</td>
<td>○</td>
</tr>
<tr>
<td>D. Data on stability (e.g. data on long-term storage test, data on severe test, data on acceleration test, etc.)</td>
<td>○</td>
</tr>
</tbody>
</table>
| 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 | ○ | △ | △ | ○ | △ |

* Contents of each data: See Appendix 1.
** Class of VMPs for application
(1) VMPs containing a new active ingredient
(2) VMPs in new route of administration
(3) VMPs in new dosage and providing a new indication
(4) New combination VMPs
(5) VMPs in similar formulation of products already approved
○: Data shall be submitted.
×: Data may be omitted.
△: Data submission shall be determined depending upon the conditions of each VMP.
Appendix 1

Example of the contents of data for a marketing approval application on quality, safety and efficacy for pharmaceutical veterinary medicinal products

A. Quality documentation
1. Active substance(s): specifications, impurities in the starting material, suitability of the manufacturing method, stereoisomerism, where relevant and stability
2. Excipients: specifications, suitability and safety data, where appropriate
3. Method of preparation: manufacturing method, in-process control tests and validation including batch analysis
4. Packaging material (immediate packaging): specifications and suitability
5. Control tests on intermediate products
6. Control tests on finished product
7. Stability of the finished product

B. Safety documentation
1. Toxicology
   a. Single dose toxicity
   b. Repeated dose toxicity
   c. Reproductive toxicity including teratogenicity
   d. Genotoxicity
   e. Carcinogenicity
   Other tests, e.g. microbiological effects on human gut flora, sensitization potential, effects on specific organ systems, where appropriate. This depends on the type of substance and use, e.g. microbiological effects on human gut flora are only required for microbiologically active substances used in food producing animals.
2. Target animal safety
3. Residue studies (only required for products food producing animals)
   a. Metabolism and residue kinetics
   b. Pharmacokinetics (absorption, distribution, metabolism, excretion)
   c. Depletion of residues
   d. Analytical method
4. Safety of users
5. Environmental impact assessment

C. Efficacy documentation
1. Pre-clinical trials (might partly already be included in safety or residues data)
2. Pharmacodynamic mechanisms underlying the therapeutic effect
3. Pharmacokinetics
4. Bioequivalence (if applicable)
5. Dose determination
6. Resistance development (antimicrobials, antiparasitics)
7. Results of clinical trials

1 Extracts from the description of “VICH and its role for authorization of veterinary medicinal products, Executive Summary (ANNEX III, A)” of reference No. 7.
### Table 4. Data Required for the Application for Approval of Veterinary Biological Products

<table>
<thead>
<tr>
<th>Category and type of data*</th>
<th>Class of drugs for application**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>A. Data on origin, details of discovery, use in foreign countries, etc.</td>
<td>○</td>
</tr>
<tr>
<td>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.)</td>
<td>○</td>
</tr>
<tr>
<td>C. Data on production</td>
<td>○</td>
</tr>
<tr>
<td>B. Data on stability (e.g. data on long-term storage test, data on stability at usage condition, etc.)</td>
<td>○</td>
</tr>
<tr>
<td>E. Data on safety for target animal</td>
<td>○</td>
</tr>
<tr>
<td>F. Data on pharmacological action (e.g. data on effectiveness, data on time for immunization and the duration, etc.)</td>
<td>○</td>
</tr>
<tr>
<td>G. Data on results of clinical trials</td>
<td>○</td>
</tr>
</tbody>
</table>

* Contents of each data: See Appendix 2
** Class of biological products for application
1. Products containing a new active ingredient or a new combination prescription drugs
2. Products in new composition of the approved ingredient
3. Products in new route of administration
4. Products providing a new indication
5. Products 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. Products in similar formulation of products already approved
   ○: Data shall be submitted.
   ×: Data may be omitted.
   △: Data submission shall be determined depending upon the conditions of products.
Appendix 2  Example of the contents of data for a marketing approval application on quality, safety and efficacy for veterinary vaccines

A. Quality documentation
1. Specific character of composition of the product
2. Method of preparation: manufacturing method, in-process control test and validation including batch analysis
3. Adjuvants and excipients: specifications, suitability and safety data, where appropriate
4. Packaging material (immediate packaging): specifications and suitability
5. Control tests during the manufacturing products
6. Control tests on finished product
7. Stability tests

B. Safety and residues documentation

B-1. Laboratory studies on:
1. Target animal safety of the administration of one dose
2. Target animal safety of the administration of an overdose
3. Examination of reproductive performance
4. Special requirements for live vaccines
   a. Spread of the vaccine strain
   b. Dissemination in the vaccinated animal
   c. Reversion to virulence of attenuated vaccines
   d. Biological properties of the vaccine strain
   e. Recombination or genomic reassortment of strains
5. Safety of users
6. Study of residues (only required for products food producing animals)
7. Interactions

B-2. Field studies
Environmental risk assessment required for veterinary medicinal products containing or consisting of Geneticaly Modified Organisms

C. Efficacy documentation
1. General requirements including the choice of antigens or vaccine strains, the efficacy of the investigating product as well as additional data such as diagnostic tests
2. Laboratory trials (well-controlled laboratory conditions by challenge)
3. Field trials (using batches representative of the manufacturing process, both safety and efficacy may be investigated in the same field study). Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.

2 Extracts from the description of “VICH and its role for authorization of veterinary medicinal products, Executive Summary (ANNEX III, B)” of reference No. 7.
4) Compliance monitoring for GLP and GCP

Data on toxicity, target animal safety or residue attached to approval application of a VMP for bovines, equines, swine, chickens, quail, honey-bees, aquatic animals for food, canines or felines has to meet the Ministerial ordinance of GLP (No. 74, Series of 1997) which is in conformity with OECD principle of GLP. And a person intending to sponsor clinical trials of a VMP for bovines, equines, swine, chickens, canines or felines shall comply with the Ministerial ordinance of GCP (No. 75, Series of 1997). A person intending to sponsor clinical trials of a new VMP shall submit prior notification of clinical trial plans to the Minister.

Staffs of the NVAL confirm contents of clinical trial plans, and inspect laboratories and clinical trial institutions in a part of examination for approval.

5) Investigation of confirmation to the GMP for VMPs

Each VMP (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 specified by the Ministerial Ordinance (No. 18, Series of 1994). Compliance with the standard of a VMP applied for approval is checked by staff of the NVAL, and they review the application through document inspection or on-site inspection. The confirmation of the VMP approved shall be renewed every 5 years.

6) Regulations on the use of living modified organisms (LMOs) for the VMPs

The use of LMOs for VMPs are regulated based on “the Act on the Conservation and Suitable Use of Biological Diversity through Regulation on the Use of LMOs (Law No. 97 Series of 2003, the so-called the Cartagena Law)”. VMPs applied recombinant organisms should be approved the use of regulations of LMOs or confirmed production facilities by the MAFF before application of marketing approval of VMPs concerned.

The Plant Products Safety Division, FSCAB, MAFF is responsible for the reception of the application of approval of the confirmation.

7. Drug Master File Registration

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, Series of 2004). It is including the name, ingredients, manufacturing methods, properties, quality or storage of the active pharmaceutical ingredient etc.

The NVAL conducts to registration affairs of drug master file. When the NVAL 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 VMP contained the registered ingredient is applied for the marketing approval, it is possible to omit a part of document to submit.

8. National Assay and National Test System

1) National assay of biological products

The VMP's 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 (Ministerial notice, No.66, Series of 1960).

Since July 2009, the Minister has not designated vaccines made under the seed lot system in principles. Only the following vaccines made under the SLS are carried on the national assay.

a) New vaccines which have not finished reexamination.

b) Vaccines against the following animal infectious diseases

Rinderpest, Epizootic encephalitis (i.e. Japanese encephalitis and West Nile virus infectious disease), Hog cholera (Classical Swine fever), High Pathogenic Avian Influenza, Newcastle disease and Rabies

The Minister designates the NVAL as an official assay laboratory in the Article 151 of the Control Regulations of Veterinary Medical Products (Ministerial ordinance No. 107, Series of 2004).

The assay is conducted on each lot or batch of product, according to the national assay standard of biological products (Ministerial notice, No.1568, Series of 2002) before marketing. Rejected products by the assay are discarded in the presence of a pharmaceutical inspector.

2) National test of diagnostics for identification of blood type, etc.
Newly approved diagnostics for identification of blood type 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.

Also when a vaccine made under the seed lot system is rejected on the spot sampling test described later, the vaccine shall be tested for every 5 lots of product at the NVAL on the basis of the Minister’s order.

3) **Spot sampling test**

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

9. **Retailing Control System**

1) **License for retailing**

Anyone shall not retail VMPs without a license for retailing of VMPs, or without a license for pharmacy. There are 47 prefectures in Japan. The governor of each prefecture grants the license for a pharmacy or a retailer of VMPs, and the license shall be renewed every 6 years.

2) **Type of seller**

Licenses of selling business for VMPs are divided into the following four types.

Type 1: Retailer at store  
Type 2: Household distributor  
Type 3: Exceptional store seller  
Type 4: Whole seller

The qualification for stuff and the category for sale of each seller are shown as following table.

<table>
<thead>
<tr>
<th>Type of License</th>
<th>Qualification for Stuff engaged</th>
<th>Category of VMPs for Sale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Retailers at store</td>
<td>Pharmacist</td>
<td>Any type of VMPs</td>
</tr>
<tr>
<td></td>
<td>Registered Salesklerk</td>
<td>Restricted VMPs designated by the MAFF</td>
</tr>
<tr>
<td>2. Household distributor</td>
<td>Pharmacist or Registered Salesklerk</td>
<td>Restricted VMPs designated by the Governor in compliance with the standard of the MAFF, such as insecticides, proprietary drugs and other drugs with mild action</td>
</tr>
<tr>
<td>3. Exceptional store seller</td>
<td>Needless</td>
<td>Restricted VMPs designated by the prefectural governor, such as VMPs having mild action, stable stability, simple usage, etc.</td>
</tr>
<tr>
<td>4. Whole seller</td>
<td>Pharmacist</td>
<td>Any type of VMPs</td>
</tr>
<tr>
<td></td>
<td>Registered Salesklerk</td>
<td>Restricted VMPs designated by the MAFF</td>
</tr>
</tbody>
</table>

The governor of the prefecture conducts the examination for qualification to retail or hand over general VMPs (exception almost all the poisonous or powerful VMPs, antibiotics, hormone, etc.) designated by the MAFF. When the successful examinee engaged in the retailer, the salesclerk shall be registered by the governor of the prefecture.

3) **Pharmaceutical supervision**

Approximately 2,000 veterinary pharmaceutical inspectors are stationed through nation, including the national government, to inspect marketing approval holders, manufacturers, and retailers of VMPs. 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 MAHs, manufacturers and drug retailers for VMPs etc. Their major duties are as follows.

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

10. Proper Application System

1) VMPs requiring directions or prescription

The Minister designates certain VMPs which need special consideration and attention by users as VMPs 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 VMPs

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

3) Restriction on use of VMPs

The Minister enacts the standard (the MAFF ordinance No. 42, Series of 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 VMPs that can be used, and its administration, dosages, and prohibition periods for use to subject animals.

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

4) VMPs requiring veterinary consultation

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

11. Post-marketing Surveillance System

1) Reexamination of new products

Data of new VMPs, which submitted for marketing approval, is not always adequate. Main reason is due to the fact that the VMPs has been tested only under controlled conditions or tested for limited cases. On the other hand, there may be useful information of new VMPs in practical use under various conditions that can be fed back to drug administration of them. Therefore, reexamination system has been established to review the efficacy and safety of a new VMPs, on the basis of results of field investigations that conducted by marketing authorization holders within 6 years after the approval of the VMP. An application for reexamination of a new VMP undergoes an investigation by the Sub-committee on reevaluation for VMPs of the Committee on Veterinary Products of the PASC.

The NVAL performs the reexamination affairs with the results of application of the VMP, spontaneous its reaction, investigations of situations of the product in foreign countries, and literature surveys conducted by the MAH of the VMP.

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

2) Reevaluation of VMP

The NVAL When quality, efficacy or safety of a VMP suspected with level of recent veterinary and pharmaceutical sciences, the product 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.

The NVAL conducts the reevaluation affairs. Staff of the laboratory collects and arranges scientific information related to quality, efficacy and safety of VMPs. Marketing authorization holders and veterinarians submit information of adverse reaction of VMPs to the NVAL. These results arranged by the NVAL are applied to select VMPs for reevaluation on the examination by the Sub-committee on reevaluation for VMPs of the Committee on Veterinary Products of the PASC.

3) Collection of adverse effects information
When marketing authorization holders of VMPs are informed of any adverse reaction, etc. as specified by MAFF ordinance for their marketed products, they must report it to the Minister.

And when veterinarians or other health professionals learns, with respect to VMPs of occurrence of any disease, disability or death suspected to be caused by adverse reactions of the product or by any other reasons, or infectious disease that it is necessary to prevent occurrence or spread of hazards to the public health and hygiene, she/he shall submit reports to the Minister.

The NVAL sorts out these reports, and release contents of adverse effects information on the website (http://www.nval.go.jp).

REFERENCE

7. VICH and its role for authorization of veterinary medicinal products Exective Summary, VICH/10/008, 5 May 2010, Final. (Website: http://www.vichsec.org)