Outline of the Regulatory System of Veterinary Drugs in Japan
Assurance of the Quality, Efficacy, and Safety Based on the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices

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Contents

List of Abbreviations--------------------------------------------------------------- 2
1. Organizations and Affairs under Jurisdiction for Animal Pharmaceutical Administration ------------------------------------------------------ 3
2. Outline of the System for Ensuring the Quality, Efficacy, and Safety of Veterinary Drugs Based on the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices------------------------------------------ 4
3. Licensing System for the Manufacturing/Marketing Business--------------------- 7
4. Licensing System for the Manufacturing Business-------------------------------- 7
5. Certifying System for Foreign Manufacturers-------------------------------------- 8
6. Approval System for Manufacturing/Marketing------------------------------------- 8
7. Drug Master File System for Veterinary Drug Substances------------------------- 14
8. National Assay/Inspection System------------------------------------------------ 14
9. Distribution Management System-------------------------------------------------- 14
10. Proper Use System-------------------------------------------------------------- 15
11. Post-marketing Survey System---------------------------------------------------- 16

References------------------------------------------------------------------------ 16

Revised in October 2015
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMP for VMPs related to the Structure and Facilities</td>
<td>The ministerial ordinance (No. 35, Series of 2005) of the structure and facilities of the factory</td>
</tr>
<tr>
<td>Minister</td>
<td>Minister of Agriculture, Forestry and Fisheries</td>
</tr>
<tr>
<td>Control Regulations</td>
<td>Control Regulations of Veterinary Medical Products (No. 107, Series of 2004)</td>
</tr>
<tr>
<td>PAFSC</td>
<td>Pharmaceutical Affairs and Food Sanitation Council</td>
</tr>
<tr>
<td>ADI</td>
<td>Acceptable Daily Intake</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice (No. 75, Series of 1997)</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice (No. 74, Series of 1997)</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice (No. 18, Series of 1994)</td>
</tr>
<tr>
<td>GPSP</td>
<td>Good Post-marketing Study Practice (No. 34, Series of 2005)</td>
</tr>
<tr>
<td>GQP</td>
<td>Good Quality Practice (No. 19, Series of 2005)</td>
</tr>
<tr>
<td>GVP</td>
<td>Good Vigilance Practice (No. 20, Series of 2005)</td>
</tr>
<tr>
<td>MRL</td>
<td>Maximum Residue Limit</td>
</tr>
<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OIE</td>
<td>International Epizootic Office: World Organization for Animal Health</td>
</tr>
<tr>
<td>VICH</td>
<td>International Cooperation on Harmonisation of Technical Requirements for Veterinary Medicinal Products</td>
</tr>
<tr>
<td>SL vaccine</td>
<td>Vaccines manufactured by using the seed-lot system</td>
</tr>
</tbody>
</table>
1. Organizations and Affairs under Jurisdiction for Animal Pharmaceutical Administration

The Ministry of Agriculture, Forestry and Fisheries (MAFF) holds jurisdiction over affairs concerning veterinary medicinal products (VMPs) (drugs intended for use only in animals) based on the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices (Law No. 145, 1960). The Ministry of Health, Labor and Welfare (MHLW) holds jurisdiction over affairs concerning human drugs.

National government organizations and affairs under jurisdiction concerning veterinary medicinal products (VMPs) are as follows:

(1) Animal Products Safety Division (APSD) of the Food Safety and Consumer Affairs Bureau (FSCAB), MAFF (supervising section on laws and regulations of animal pharmaceutical affairs)

- Planning of regulation and operation concerning risk management of VMPs
- Control of manufacturing/marketing approval of VMPs
- Licensing of the manufacturing/marketing business and manufacturing business on VMPs
- Certification of foreign manufacturers of VMPs
- Pharmaceutical supervision, guidance

(2) Fish and Fishery Products Safety of APSD of FSCAB, MAFF

- Approval review of fishery products
- Guidance for the proper use of fishery products

(3) MAFF National Veterinary Assay Laboratory (NVAL) (an organization responsible for the technical response for animal pharmaceutical affairs)

- Approval review, reexamination and reevaluation of VMPs
- GMP compliance review of VMPs
- GLP/GCP compliance review of VMPs
- National assay, inspection
- Distribution of the reference standard for assay
- Technical guidance
- Research for regulatory science
- International technical cooperation (OIE Collaborating Centers, activities of the Expert Working Group of VICH)

(4) PASC, PAFSC: Council for VMPs (a council on VMPs)

- Investigation/discussion on important considerations concerning pharmaceutical affairs

  Agenda: Approval of new VMPs, reexamination/reevaluation of drugs
           Establishment of standards for veterinary medicinal products
           Establishment of standards for use of drugs for food-producing animals (Use prohibition period)

(5) Other concerned sections on VMPs

  (i) Animal Health Division, FSCAB, MAFF
2. Outline of the System for Ensuring the Quality, Efficacy, and Safety of Veterinary Drugs Based on the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices

VMPs are regulated by the concerned regulations including the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, Enforcement Ordinance of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices (Enforcement Ordinance No. 11, 1961), and the Control Regulations of Veterinary Medical Products (Control Regulations, Ministerial Ordinance No. 107, 2004).

The outline of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices concerning VMPs is as follows:

(1) Substitution rules for veterinary medicinal drugs

For medicinal products intended for use only in the animals in the law, the “Minister of Health, Labor and Welfare” and “MHLW Ordinance” are substituted with the “Minister of Agriculture, Forestry and Fisheries” and “MAFF Ordinance”, respectively. (Article 83)

(2) Purpose

To improve health/hygiene by implementing the necessary regulations to ensure the quality, efficacy, and safety of drugs, quasi drugs, cosmetics (except for veterinary drugs), medical devices and devices used for regenerative medicine. (Article 1)

(3) License for the manufacturing/marketing business and manufacturing business

A person who intends to manufacture/market drugs shall obtain a license for the manufacturing/marketing business. The Minister of Agriculture, Forestry and Fisheries (the Minister) may provide a license for manufacturing/marketing VMPs. (Article 12)

No person who does not receive the license for the manufacturing business of drugs shall manufacture drugs as a business. The Minister may provide licensing by manufacturing site according to the category specified in the MAFF Ordinance. (Article 13)

Foreign manufacturers of drugs may obtain the certification of the Minister. The Minister may provide...
certification by manufacturing site according to the category specified in the MAFF Ordinance. (Article 13-3)
✧ A person who intends to market VMPs shall obtain approval of the Minister by marketed product. (Article 14)
✧ Marketing authorization holders (MAHs) of new drugs shall undergo reexamination 6 years after approval (Article 14-4). Of the other existing approved drugs, the drugs specified by the Minister shall be reevaluated. (Article 14-6)
✧ Manufacturers may register the name, component, method of preparation, property, quality and storage in the Drug Master File. (Article 14-11)

(4) Licensing of the medicament marketing business
✧ A person who intends to run a pharmacy and medicament marketing business shall get licensing from the governor of the prefecture where the store is located. (Article 4, Article 24)

(5) Standards and assays of drugs
✧ The Minister of Health, Labor and Welfare shall establish the Japanese Pharmacopoeia. (Article 41)
✧ The Minister shall establish the product standards. (Article 42)

(6) Handling, advertisement and supervision
✧ Distribution and misleading advertising of adulterated drugs, mislabeling drugs, unapproved drugs and unassayed drugs are banned. (Article 55, Article 56, Article 66)
✧ Supply of proper drugs is secured through national assay, on-site inspection and national inspection. (Article 43, Article 69, Article 71)
✧ Openers of a pharmacy or distributors of drugs shall not sell or provide drugs specified by the Minister to persons other than those for whom veterinarians issue prescriptions or give instructions. (Article 49)

(7) Reporting of adverse drug reaction
✧ When MAHs learn about an adverse drug reaction specified by the MAFF Ordinance for the drugs they handle, they shall inform the Minister of the fact. (Article 68-10)

(8) Clinical studies
✧ This law system regulates the compliances required for persons who intend to request clinical studies. (Article 80-2)

(9) Handling of VMPs
✧ Ban on manufacturing and importing VMPs without licensing: Principally, manufacturing and importing VMPs are banned. (Article 83-2)
✧ Ban on use of unapproved drugs: Principally, unapproved drugs shall not be used for food-producing animals. (Article 83-3)
✧ Regulation on use of VMPs: The Minister may specify regulations on the use of drugs used for food-producing animals. (Article 83-4, Article 83-5)
The above-mentioned various regulations from the development of VMPs to the post-marketing survey based on the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices are provided in Figure 1.
Figure 1 Various Systems for VMPs Based on the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices

I. Development test and approval system for manufacturing/marketing
   - Approval for manufacturing/marketing GLP, GCP, GMP
   - Registration of drug substances
   - Japanese Pharmacopoeia product standards

II. Licensing system for the manufacturing/marketing business & licensing system for the manufacturing business
   - License for manufacturing/marketing business GQP, GVP
   - License for manufacturing business GMP (building/facilities)
   - Licensing of foreign manufacturing sites GMP (building/facilities)

III. Distribution Management System
   - License for pharmacy/selling business of drugs
   - Regulations of management and buildings/facilities of pharmacy/selling business
   - Regulations on selling of drugs requiring prescription
   - Regulations for use of drugs for food-producing animals (standards for use)

IV. Evaluation Control System
   - Reexamination system GPSP
   - Reevaluation system GPSP
   - Reporting system of adverse reactions

<Remarks>
GLP: Good laboratory practice
GCP: Good clinical practice
GMP: Good manufacturing practice
GMP (building and facilities): Rules on building/facilities of manufacturing site
GQP: Good quality practice
GVP: Good vigilance practice
GPSP: Good post-marketing study practice
3. Licensing System for the Manufacturing/Marketing Business

(1) Licensing procedures

The license of manufacturing/marketing of VMPs corresponding to the drug types provided in Table 1 should be obtained for selling manufactured/imported drugs (except for drug substances). Applicants should submit the license application of the manufacturing/marketing business corresponding to the drug types they would handle to the Minister through the governor of the prefecture where the office with the major function is located.

The license application of the manufacturing/marketing business is reviewed at APSD of FSCAB, MAFF based on the submitted documents from the applicant, and the Minister shall provide the license by the types shown in Table 1. The process of the licensing procedure usually takes 6 months. However, this does not include the period required to prepare a response to instructions on the correction of defects in the application and attached documents.

This license is updated every 5 years. The process for updating the license takes 3 months.

Table 1 Relationship between types of drugs and types of licenses for the manufacturing/marketing business

<table>
<thead>
<tr>
<th>Types of drugs</th>
<th>Types of licenses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription drugs (drugs specified in Paragraph 1, Article 49 of the Law)</td>
<td>First type of manufacturing/marketing license holder</td>
</tr>
<tr>
<td>Drugs other than prescription drugs</td>
<td>Second type of manufacturing/marketing license holder</td>
</tr>
</tbody>
</table>

(2) License requirements for the manufacturing/marketing business

MAHs of VMPs should assign a pharmacist as a general marketing compliance officer who is responsible for quality control and post-marketing safety assurance of drugs (However, if only biological products are marketed, a person who has expertise in bacteriology such as a physician or veterinarian is possible.). In order to obtain the license for the manufacturing/marketing business, the factory and the store should conform to the MAFF Ordinance on Good Quality Practice (GQP Ordinance, No. 19, Series of 2005) and the MAFF Ordinance on Good Vigilance Practice (GVP Ordinance, No. 20, Series of 2005).

The prefectural governor shall have a veterinary pharmaceutical inspector conduct an on-site inspection in the principal business facility at the time of the license application (license update) for the manufacturing/marketing business and determine whether the business system is in accordance with the GQP Ordinance and GVP Ordinance, then submit the result to the Minister.

4. Licensing System for the Manufacturing Business

(1) License classification and procedures of the manufacturing business
A person who manufactures drugs as a business should obtain the license for the manufacturing business. The license guarantees the quality of manufactured drugs, quality control and storage facilities.

The Minister provides the license for the manufacturing business depending on the types of drugs manufactured and the manufacturing processes by the classification provided in Table 2. Applicants should submit the license application of the manufacturing business corresponding to the classification in Table 2 to the Minister through the governor of the prefecture where the manufacturing facility is located.

APSD of FSCAB, MAFF shall review the eligibility of the applicant and manufacturing administrator of the manufacturing facility and the appropriateness of the building and facilities of the manufacturing site. The process of the licensing procedure for manufacturing drugs usually takes 6 months. However, this does not include the period required to prepare a response to instructions on the correction of defects in the application and attached documents.

This license is updated every 5 years. The process for updating the license takes 3 months.

### Table 2 Relationship between the classification of VMPs manufacturing business and drugs manufactured/manufacturing process

<table>
<thead>
<tr>
<th>Classification of manufacturing facility</th>
<th>Types of drugs manufactured and the manufacturing processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All/part of the manufacturing process of the following drugs (i) Biological products (except for in-vitro diagnostic reagent) (ii) Target drugs for assays (except for (i)) (iii) Gene-recombinant drugs (except for classification 3), etc.</td>
</tr>
<tr>
<td>2</td>
<td>All/part (except for classification 4) of the manufacturing process of sterile pharmaceutical products (except for classification 1 and 3)</td>
</tr>
<tr>
<td>3</td>
<td>All/part of the manufacturing process other than that of the classification of 1 and 2 (except for classification 4)</td>
</tr>
<tr>
<td>4</td>
<td>Only packaging/labelling/storage (except for classification 1)</td>
</tr>
</tbody>
</table>

### (2) License requirements for the manufacturing business

In order to obtain the license for the manufacturing business, each factory should conform to the rules specified in the ministerial ordinance (No. 35, Series of 2005) of the structure and facilities of the factory (GMP for VMPs related to the Structure and Facilities).

The prefectural governor shall have a veterinary pharmaceutical inspector conduct an on-site inspection in the principal factory at the time of the license application (license update) for the manufacturing business and determine whether the building and facilities are in accordance with the Regulations for Buildings and Facilities, then submit the result to the Minister.

In addition, drug manufacturers should assign a pharmacist as a manufacturing administrator at each factory (However, if only biological products are marketed, a person who has expertise in bacteriology
such as a physician or veterinarian is possible).

5. Certifying System for Foreign Manufacturers

A person who intends to manufacture VMPs in foreign countries which are to be imported to Japan (foreign manufacturer) can obtain certification from the Minister. The Minister shall provide the certification of the foreign drug manufacturer at each factory in accordance with the same classification of the manufacturing business license of VMPs provided in Table 2.

In order to obtain the certification of the foreign drug manufacturer, each factory should conform to the rules specified in the Regulations for Buildings and Facilities.

APSD of FSCAB, MAFF shall review the certification of foreign drug manufacturers. The process of the certification procedure usually takes 6 months.

This certification is updated every 5 years. The process for updating the certification for foreign drug manufacturers takes 3 months.

6. Approval System for Manufacturing/Marketing

(1) Approval procedures

MAFF implements the approval review of a drug to be manufactured/marketed for name, components/amount, manufacturing process, dose and administration, indications and adverse reactions by product based on documents submitted by the applicant. MVAL is responsible for the approval review activities. Drug approval guarantees the quality, efficacy, and safety of a drug product.

The Minister provides approval for manufacturing/marketing on the assumption that a drug is manufactured at a licensed factory or certified foreign factory.

Review of new VMPs is firstly implemented through investigation and discussion by each Advisory Committee (biological products, antimicrobial products, general medicaments or fishery products) of PASC, PAFSC: Council for VMPs, depending on the types of applied products. Drugs used for food-producing animals are reviewed for persistence by the Persistence Advisory Committee of VMPs. After completion of the review in the Advisory Committee, the Council for VMPs starts its review. If the chairperson of the Sub-council determines the need to review cautiously based on the opinion of the Council in terms of the indications, toxicity and adverse reactions of the applied drug, then the Pharmaceutical Affairs Sub-council shall review the approval.

The Minister of Health, Labor and Welfare sets the maximum residue limit (MRL) of VMPs in food products.

The Food Safety Commission, Cabinet Office, is responsible for the human health effects assessment of drugs used for food-producing animals. The Food Safety Commission sets the acceptable daily intake (ADI) of the components of VMPs.

After a final decision is made that approval is acceptable following the completion of all these
reviews/assessments, the specified procedures are performed and the application is approved.

The process of the approval procedure usually takes 12 months. However, this does not include the period required to prepare a response to instructions on the correction of defects in the application and attached documents or instructions by PAFSC.

(2) Product standards

The following 3 types of product standards are established based on Article 42 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices.

(i) National assay standard of biological products (Ministerial notice, No. 1567, Series of 2002)
(ii) Standard of antibiotics for animals (Notice No. 1123, Series of 1999)
(iii) Standards for veterinary biological materials (Notice No. 1911, Series of 2003)

Drugs specified in the product standards should conform to each standard.

NVAL prepares the draft revision of these standards.

(3) Documents required for approval application

A drug approval review is implemented based on the documents submitted by an applicant. Documents required for the application differ depending on whether a new active ingredient is included or the ingredient is the same as the existing approved drugs. Documents which should be submitted at the time of application for VMPs are provided in Table 3 and Table 4. A sample of the content of each attached document is provided in Appendix 1 and Appendix 2.

Various guidelines have been established for the test procedures to prepare these documents. Besides, various VICH guidelines on quality, safety, and efficacy have been established since the initiation of VICH’s activities in 1996, mainly consisting of Japan, the United States and the EU, for the purpose of international harmonization of technical requirements for approval of VMPs.

(4) GMP compliance inspection for VMPs

The procedures of manufacturing control and quality control at a factory of VMPs (including drug substances) should conform to the rules specified in the ministerial ordinance for manufacturing control and quality control of VMPs (GMP Ordinance No. 18, Series of 1994). After the application for approval, the compliance of VMPs to this Ordinance is reviewed by NVAL staffs and is confirmed by documents and an on-site inspection based on the application of compliance inspection submitted at the time of the application for approval. GMP compliance of the approved drug is verified every 5 years.

(5) Compliance inspection on standards for reliability of application data (GLP and GCP)

Data on the toxicity, safety of target animals or persistence attached to the application documents of drugs used for cows, horses, pigs, chickens, quails, honeybees, aquatic animals farmed for providing food, dogs or cats, should be collected and prepared in accordance with the Ordinance on Good Laboratory Practice for the safety of VMPs (GLP Ordinance: Ministerial Ordinance No. 74, Series of 1997) according to OECD’s “Principle of Good Laboratory Practice (GLP principle)”.

A person who intends to perform a clinical study of drugs using cows, horses, pigs, dogs or cats should
follow the Good Clinical Practice on VMPs (GCP Ordinance No. 75, Series of 1997).

Besides, a person who intends to request a clinical study of new VMPs should submit notification of the clinical study addressed to the Minister to NVAL beforehand.

The staff of NVAL shall confirm the contents of the notification for the clinical study and perform an inspection based on the documents or an on-site inspection to confirm the compliance of the documents to GLP and GCP.

(6) Regulation for use of living modified organisms concerning VMPs

Use of living modified organisms (LMOs) with viability concerning VMPs is regulated based on the “Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms” (Law No. 97, 2003, so-called Cartagena Law). MAFF shall approve the rules for use or confirm the manufacturing facilities before the approval application for manufacturing/marketing for VMPs using LMOs.

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

Table 3 Scope of data which should be attached at the time of the application for VMPs except for biological products

<table>
<thead>
<tr>
<th>Type of data*</th>
<th>Drug application category**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>A. Origin or development history, usage situation in foreign countries</td>
<td>○</td>
</tr>
<tr>
<td>B. Physical-chemical test data (e.g. structure determination, physical-chemical property, specifications and assay procedures)</td>
<td>○</td>
</tr>
<tr>
<td>C. Data on manufacturing processes</td>
<td>○</td>
</tr>
<tr>
<td>D. Study data on safety (e.g. long-term storage test, stress test, accelerated test)</td>
<td>○</td>
</tr>
<tr>
<td>E. Data on toxicity test</td>
<td></td>
</tr>
<tr>
<td>1. Acute toxicity test</td>
<td>○</td>
</tr>
<tr>
<td>2. Subacute toxicity test and chronic toxicity</td>
<td>○</td>
</tr>
<tr>
<td>3. Special toxicity test (e.g. teratogenicity, local tolerance)</td>
<td>△</td>
</tr>
<tr>
<td>F. Safety test data in target animals</td>
<td>○</td>
</tr>
<tr>
<td>G. Data of pharmacology test</td>
<td></td>
</tr>
<tr>
<td>1. Test as evidence of efficacy</td>
<td>○</td>
</tr>
<tr>
<td>2. General pharmacology test</td>
<td>○</td>
</tr>
<tr>
<td>H. Test data on absorption, distribution, metabolism and elimination</td>
<td>○</td>
</tr>
<tr>
<td>I. Data on clinical studies</td>
<td>○</td>
</tr>
<tr>
<td>J. Data on persistence</td>
<td>○</td>
</tr>
</tbody>
</table>

* See Appendix 1 for an example of the content of each document
** Application category of drugs
(1) A drug containing a new active ingredient
(2) A drug with a new dosage regimen
(3) A drug with a new dose and drugs with new indications
(4) A drug with a new combination of active ingredients
(5) A drug which is identical to the existing VMPs
○: Data requiring attachment
×: Data not requiring attachment
△: Data for which requirement for attachment shall be determined depending on each drug
Appendix 1

Examples of attachments on quality, safety, and efficacy in the application for VMPs except for biological products

A. Data on quality
1. Active ingredients: characteristics, purity of starting materials, compliance of manufacturing process, stereoisomers and isomers concerned
2. Additives: data on characteristics, compliance, and safety as necessary
3. Manufacturing process: manufacturing process, quality test at the intermediate stage and validation including analytical test of the manufactured lot
4. Packaging materials (direct packaging): characteristics and compliance
5. Quality control test of intermediate products
6. Quality control test of final products
7. Stability of final products

B. Data on safety
1. Toxicological test
   a. Single dose toxicity
   b. Repeated dose toxicity
   c. Reproductive toxicity including teratogenicity
   d. Genotoxicity
   e. Carcinogenicity
      Other tests which are considered to be appropriate, including the microbiological effect in human intestinal bacterial flora, susceptibility or the effect on specific organs.
      This depends on the type and usage of ingredient substances. For example, a test for the effect on human intestinal bacterial flora is required only when active ingredients for the microorganisms of food-producing animals are used.
2. Safety in animals which are subject to the drug
3. Persistence test (it is required only for drugs used for food-producing animals)
   a. Metabolism and dynamics of residue
   b. Pharmacodynamics (absorption, distribution, metabolism, elimination)
   c. Elimination of residue
   d. Analytical method
4. Safety for users
5. Environmental assessment

C. Data on efficacy
1. Preclinical studies (part of this data may be included in the safety test or persistence test)
2. Pharmacodynamic mechanism which leads to the therapeutic effect
3. Pharmacokinetics
4. Bioequivalence (as appropriate)
5. Dose finding
6. Development of resistance (antimicrobial agents, insecticides)
7. Result of clinical studies

\[\text{Abstracted from ANNEX III A of VICH and its role for authorization of veterinary medicinal products Executive Summary (Reference 6)}\]
Table 4 Scope of data which should be attached at the time of the application for veterinary biological products

<table>
<thead>
<tr>
<th>Type of data*</th>
<th>Drug (biological product) application category**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)   (2)   (3)   (4)   (5)   (6)   (7)</td>
</tr>
<tr>
<td>A. Origin or development history, usage situation in foreign countries</td>
<td>○      ○      ○      ○      ○      ×</td>
</tr>
<tr>
<td>B. Physical-chemical test data (e.g. creation of a strain for manufacturing, characterization of physical-chemical property and biological property, test of specifications and assay procedures)</td>
<td>○      Δ      Δ      Δ      ○      Δ</td>
</tr>
<tr>
<td>C. Data on manufacturing processes</td>
<td>○      ○      Δ      Δ      Δ      ○      Δ</td>
</tr>
<tr>
<td>D. Study data on stability (e.g. long-term storage test, stability during usage)</td>
<td>○      ○      Δ      Δ      Δ      ○      Δ</td>
</tr>
<tr>
<td>E. Safety test data in target animals</td>
<td>○      ○      ○      Δ      Δ      ×      ×</td>
</tr>
<tr>
<td>F. Data of pharmacology test (e.g. efficacy test, timing of acquired immunity and test for persistence of efficacy)</td>
<td>○      ○      Δ      ○      ○      ×      ×</td>
</tr>
<tr>
<td>G. Data on clinical studies</td>
<td>○      ○      Δ      ○      ×      ×      ×</td>
</tr>
</tbody>
</table>

* See Appendix 2 for an example of the content of each document

** Application category of drugs
(1) A drug containing a new active ingredient and drugs with a new combination of active ingredients
(2) A drug whose active ingredient composition is different from the existing approved active ingredient composition
(3) A drug with a new dosage regimen
(4) A drug with new indications
(5) A drug with a new dose
(6) A drug whose strain for manufacturing is different from that of the existing approved drug but the property is considered to be equivalent to that of the existing approved drug in NVAL
(7) A drug which is identical to the existing VMPs
○: Data requiring attachment
×: Data not requiring attachment
Δ: Data for which requirement for attachment shall be determined depending on each drug
Appendix 2

Examples of attachments on quality, safety, and efficacy in the application for vaccines for animals

A. Data on quality
1. Characteristics of drug substances
2. Manufacturing process: manufacturing process, quality test at the intermediate stage and validation including analytical test of the manufactured lot
3. Adjuvants and excipients: data on characteristics, compliance, and safety as necessary
4. Packaging materials (direct packaging): characteristics and compliance
5. Quality control test in the manufacturing process
6. Quality control test of final products
7. Stability of final products

B. Data on safety
B-1. Test in laboratory
1. Safety of target animals by single-dose
2. Safety of target animals by high-dose
3. Test for reproductive potential
4. Special requirements for live vaccine
   a. Spread of vaccine strain (cohabiting infection)
   b. Biodistribution in vaccinated animals
   c. Confirmation of recurrence of pathogenicity in attenuated vaccine
   d. Biological property of vaccine strain
   e. Recombination or genetic reassortment of vaccine strain
5. Safety for users
6. Interaction

B-2. Field test
A field evaluation is needed for a vaccine for animals which contains genetically modified organisms as a component or active ingredient.

C. Data on efficacy
1. General requirements including selection of antigen or vaccine strain and an additional test, including not only the efficacy of the tested product but also the diagnostic procedures
2. Laboratory test (attack in a well-controlled test condition)
3. Field test (research in the identical field test for safety and efficacy which are confirmed using representative products in the manufacturing process). Even if efficacy is not confirmed in the laboratory test, efficacy may be confirmed only in the field test.

2 Abstracted from ANNEX III B of VICH and its role for authorization of veterinary medicinal products Executive Summary (Reference 6)
7. Drug Master File System for Veterinary Drug Substances

A person who manufactures drug substances (including those who manufacture drug substances abroad) can apply for registration on the Drug Master File regarding the name, ingredients, manufacturing procedure, property, quality, storage and other matters specified based on the Ordinance (Ministerial Ordinance No. 107, Series of 2004) of the drug substances. NVAL is responsible for the registration procedure of drug substances. NVAL shall review the application documents and give public notice of the registry number, date of registry, name of the registered contractor of drug substances, address and name of the product when registration on the Drug Master File is completed.

Part of the approval application documents may be omitted for a drug whose drug substance has already been registered.

8. National Assay/Inspection System

(1) National assay for biological products

Drugs specified by the Minister should undergo national assay. Biological products requiring high-level manufacturing techniques and the assay procedure (vaccine, serums and diagnostic agents for infectious diseases) have been specified as the target drugs (Notice No. 66, Series of 1961).

Vaccines manufactured using the seed-lot system (SL vaccine) are principally excluded from the assay. However, the following vaccines have to undergo the assay.

(i) New vaccines for which reexamination is not completed
(ii) Vaccines for the following domestic animal infectious diseases

- Rinderpest, epizootic encephalitis (Japanese encephalitis, West Nile virus infectious disease),
- classical swine fever, avian influenza, Newcastle disease and rabies

The Minister has designated NVAL as an assay-implementing organization in Article 151 of the Control Regulations of Veterinary Medical Products. The assay shall be implemented by production lot before marketing according to the rules of the national assay standard of biological products (Notice No. 1568, Series of 2002). Pharmaceutical products which are judged to be unacceptable in the assay shall be discarded with a pharmaceutical inspector present.

(2) Assay by assay order

For antibodies for blood typing newly approved for manufacturing/marketing, 30 lots or products for 2 years shall undergo assay by NVAL by order of the Minister. Pharmaceutical products which are judged to be unacceptable in the assay shall be discarded.

Besides, for SL vaccines which are judged to be unacceptable in the after-mentioned spot sampling test, the products of 5 lots, which are to be marketed later, shall undergo the assay by NVAL by order of the Minister.
(3) Spot sampling test

In order to eliminate defective drugs at the manufacturing/marketing stages and assure the drug quality, pharmaceutical inspectors of NVAL shall implement a quality test for drugs sampled from factories and marketing locations. Pharmaceutical products whose quality is judged to be unacceptable in the assay shall be recovered and discarded.

9. Distribution Management System

(1) Licensing of the marketing business for drugs

No one can sell VMPs without the pharmacy license or marketing business license for drugs. Forty-seven prefectural governors grant licenses to pharmacies at each location or marketing business for VMPs. The license is updated every 6 years.

(2) Types of marketing businesses for drugs

Prefectural governors shall grant the license of the marketing business for VMPs according to the 4 types of classifications ((i)Retailer at a store, (ii)Household distributor, (iii)Exceptional store seller, (iv)Wholesaler) provided in Table 5. The requirements of these distributors of VMPs and the scope of drugs marketed are provided in Table 5.

Table 5 Types of marketing businesses for drugs and their marketing requirements

<table>
<thead>
<tr>
<th>Name of marketing business</th>
<th>Qualification of sales clerk</th>
<th>Scope of drugs marketed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Retailer at a store</td>
<td>Pharmacist</td>
<td>All types of drugs</td>
</tr>
<tr>
<td></td>
<td>Registered sales clerk</td>
<td>Drugs other than restricted VMPs(drugs for which only a pharmacist can handle)</td>
</tr>
<tr>
<td>(ii) Household distributor</td>
<td>Pharmacist or registered sales clerk</td>
<td>Drugs which require no special conditions for mild effects and storage (resistant to secular change), can be handled by a sales clerk without knowledge of pharmaceutical products, and conform to the standards specified in the Ordinance (excluding restricted VMPs)</td>
</tr>
<tr>
<td>(iii) Exceptional store seller</td>
<td>No qualification required</td>
<td>Restricted to drugs assigned by the prefectural governors who grant the license (drugs which are easy for mild effects, stable storage and usage, and whose containers or packages are tough)</td>
</tr>
<tr>
<td>(iv) Wholesaler</td>
<td>Pharmacist</td>
<td>All types of drugs</td>
</tr>
<tr>
<td></td>
<td>Registered sales clerk</td>
<td>Drugs other than restricted drugs</td>
</tr>
</tbody>
</table>

Prefectural governors shall conduct an examination of the qualification with which a person can sell or provide general medicaments other than drugs assigned by the Minister (almost all poisonous drugs, powerful drugs, antibiotics, and hormone preparations).

When a person who has passed this examination works on marketing drugs, he/she has to be registered by the prefectural governors.
(3) Pharmaceutical supervision

About 2000 veterinary pharmaceutical inspectors including national inspectors are assigned all over Japan in order to monitor/supervise the facilities for manufacturing/marketing, manufacturing and retailing VMPs. Prefectural veterinary pharmaceutical inspectors are those staff belonging to the Livestock Division, Livestock Hygiene Service Centers, etc.

Veterinary pharmaceutical inspectors constantly conduct on-site inspections in facilities of MAHs of medicinal drugs, drug manufacturers and drug distributors for monitoring. The main tasks of the veterinary pharmaceutical inspector are as follows:

(i) Compliance inspection for GQP, GVP and the Regulations for Buildings and Facilities (on-site inspection)

(ii) Monitoring of unapproved/unlicensed medicinal/defective medicinal drugs and falsely labeled products

(iii) Control of fallaciousness, excessive advertising and distribution without license

10. Proper Use System

(1) VMPs requiring directions or prescription

The Minister has assigned some drugs which require special consideration and caution for users as those requiring directions or prescription by veterinarians at the time of delivery (VMPs requiring directions or prescription). For example, antibiotics, hormone preparations and vaccines used for cows, horses, sheep, goats, pigs, dogs, cats and chickens are included in these assigned drugs.

(2) Ban on use of unapproved drugs

No one should use unapproved drugs in food-producing animals (cows, horses, pigs, chickens, quails, honeybees and farm-raised aquatic animals), except when these drugs are used for research or used for other purposes specified based on the Ordinance (Ministerial Ordinance No. 70, Series of 2003).*

(3) Restrictions for VMPs usage

The Minister has specified the usage standard based on the Restriction for the Usage of VMPs and MPs (Ministerial Ordinance No. 43, Series of 2013) to ensure the safety in public health when administering antimicrobial products, etc., to food-producing animals. This standard includes animals for which the drug can be used, dosage and administration, and the use prohibition period for the target animals.

* Usage of unapproved drugs containing substances for which the residue standard cannot be established, VMPs and drugs for humans for food-producing animals is prohibited due to concerns over any effects of carcinogenicity on human health.

(4) System for drugs requiring examination

Veterinarians should not administer or prescribe powerful drugs, biological products, drugs requiring direction or drugs specified in the Restriction for the Usage of VMPs and MPs without their examination (Article 18 of the Veterinary License Law [Law Number 186, Year 1949]).
11. Post-marketing Survey System

(1) Reexamination of new drugs

Data submitted at the time of manufacturing/marketing of new drugs may not necessarily be adequate mainly because data obtained from results in limited animal cases under controlled test conditions may be limited. Meanwhile, there can be useful data under various post-approval conditions for which we can provide feedback on the usage of drugs. Therefore, the reexamination system has been established in which the efficacy and safety of new drugs are reviewed based on the field research results of new drugs conducted by MAHs for 6 years after approval. New drugs for which reexamination applications are submitted shall be investigated and discussed by the VMPs Reevaluation Advisory Committee of PASC, PAFSC: Council for VMPs.

NVAL conducts reexamination procedures based on the usage results of the drugs, status of adverse reactions, status of the drugs in foreign countries and documents by a literature search prepared by MAHs of the new drugs. Application materials for reexamination should be collected and prepared according to the Good Post-marketing Study Practice (GPSP) for VMPs (GPSP Ordinance, Ministerial Ordinance No. 33, Series of 2005). The staff of NVAL shall conduct research on compliance of the materials to GPSP.

(2) Reevaluation of drugs

When the quality, efficacy, or safety of a drug is suspected from the viewpoint of current scientific levels of veterinary medicine and pharmaceutical science, the drug should undergo reevaluation by the direction of the Minister. Materials for reevaluation should also be collected and prepared according to the GPSP Ordinance.

NVAL conducts the reevaluation procedures. The staff of NVAL collect and organize the information of scientific literature on the efficacy and safety of VMPs and information of adverse drug reactions reported from MAHs and veterinarians. Results following organizing the information are used for investigation/discussion to select the target substance for reevaluation by the VMPs Reevaluation Advisory Committee of PASC, PAFSC: Council for VMPs.

(3) Information collection system on adverse reactions

When MAHs notice any adverse reactions specified by MAFF’s ordinance for a drug they handle, they shall communicate that fact to the Minister.

Besides, when concerned persons in charge of medicinal products including veterinarians notice the matters on occurrences of diseases, impairments or death suspected to be caused by the adverse reactions or other reasons or occurrences of infections suspected to be caused by the usage of the drug, and they identify the necessity for prevention of the occurrence or expansion of the public health hazard, they shall communicate that fact to the Minister.

NVAL organizes the information of these adverse reaction reports and provides the contents on their website (http://www.nval.go.jp).