Herbal Medicine for Animal Use in JAPAN

Quality Assay Section,
Assay Division II,
National Veterinary Assay Laboratory

Veterinary Drugs

Veterinary Pharmaceuticals

- General medicines
  - Herbal medicines
  - Vitamins
  - Hormones
  - Digestive medicines
  - Anti-inflammatory agents
  - Disinfectants / Antiseptics
  - Pesticides for animal etc.

Antimicrobial medicines

Vaccines, Toxoids, Antiserums

Veterinary Biologics

Diagnostic reagents
<table>
<thead>
<tr>
<th>Risk Management of Veterinary Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre Marketing</strong></td>
</tr>
<tr>
<td>➢ Marketing Approval System</td>
</tr>
<tr>
<td><strong>Post Marketing.</strong></td>
</tr>
<tr>
<td><strong>Manufacturing &amp; Quality Control</strong></td>
</tr>
<tr>
<td>➢ License of the Manufacturer</td>
</tr>
<tr>
<td>➢ License of the Marketing Authorization Holders</td>
</tr>
<tr>
<td><strong>Distribution Control</strong></td>
</tr>
<tr>
<td>➢ License of the Retailer</td>
</tr>
<tr>
<td>➢ System for Drugs Requiring Veterinary Consultation</td>
</tr>
<tr>
<td>➢ Prescription system</td>
</tr>
<tr>
<td><strong>Use Control</strong></td>
</tr>
<tr>
<td>➢ Restrictions on the Usage of Veterinary Drugs</td>
</tr>
<tr>
<td><strong>Review of Marketing Approval</strong></td>
</tr>
<tr>
<td>➢ Reexamination &amp; Reevaluation</td>
</tr>
<tr>
<td>➢ Reporting Adverse Reactions</td>
</tr>
</tbody>
</table>
Marketing Approval System

Nobody can sell veterinary drugs without Marketing Approval.

<table>
<thead>
<tr>
<th>Requirements of the approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ License of the Marketing Authorization Holders</td>
</tr>
<tr>
<td>✓ License of the Manufacturer</td>
</tr>
<tr>
<td>✓ Management of manufacture conformed to GMP (Good Manufacturing Practice)</td>
</tr>
<tr>
<td>✓ Data for Marketing Approval</td>
</tr>
</tbody>
</table>
  - Data conformed to GLP (Good Laboratory Practice) |
  - Data conformed to GCP (Good Clinical Practice) |
Data Required for Marketing Approval of a Veterinary Drug in Japan

Origin & background of discovery

Physicochemical properties

Stability

Toxicity (GLP)

Production protocol

Pharmacological action

Absorption, Distribution, Metabolism, Excretion

Clinical trials (GCP)

Target animal safety (GLP)

Examination

Residues (GLP)

Approval
<table>
<thead>
<tr>
<th>Data No.</th>
<th>Data category</th>
<th>(A) New herbal medicine</th>
<th>(B) New compositions</th>
<th>(C) New administration route</th>
<th>(D) New dosage/indications</th>
<th>(E) Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Origin &amp; background of discovery</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>×</td>
</tr>
<tr>
<td>2</td>
<td>Physicochemical properties</td>
<td>○</td>
<td>○</td>
<td>△</td>
<td>△</td>
<td>○</td>
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<tr>
<td>3</td>
<td>Production protocol</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>4</td>
<td>Stability</td>
<td>○</td>
<td>○</td>
<td>△</td>
<td>△</td>
<td>○</td>
</tr>
<tr>
<td>6</td>
<td>Toxicity</td>
<td>△</td>
<td>△</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>7</td>
<td>Repeat (Chronic etc.)</td>
<td>△</td>
<td>△</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>8</td>
<td>Specific</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>×</td>
<td>×</td>
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<tr>
<td>9</td>
<td>Target animal safety</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>×</td>
</tr>
<tr>
<td>10</td>
<td>Pharmacological action</td>
<td>△</td>
<td>△</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>11</td>
<td>Efficacy</td>
<td>△</td>
<td>△</td>
<td>×</td>
<td>×</td>
<td>×</td>
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<tr>
<td>12</td>
<td>General</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>×</td>
</tr>
<tr>
<td>14</td>
<td>Clinical trial</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>×</td>
</tr>
<tr>
<td>15</td>
<td>Residue</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>×</td>
</tr>
</tbody>
</table>

(note) ○: Data must be attached
△: It shall not be necessary to attach the data
×: Data shall not be necessary to attach
No veterinarian should provide or prescribe poisonous or powerful drugs, etc., without providing consultation by themselves.

① Poisonous drugs
② Powerful drugs
③ Biologics (vaccines, serums)
④ Prescription drugs
   (Vaccines, Antimicrobial medicines, Hormonal products, etc.)
⑤ Drugs regulated for use on animals
   (Antimicrobial medicines, Hormonal products)

Veterinary drugs used for fish is not included in this system.
Prescription System

Drug distributor

① Consulting

② Issue of prescription by the result of diagnosis

③ Order by prescription

④ Selling of veterinary drugs

⑤ Reasonable and safe use of veterinary drugs

Veterinary drugs used for fish is not included in this system.
### Use Control

**Restrictions on the Usage of Veterinary Drugs**

Standards governing restrictions on the usage of veterinary drugs used for food-producing animals to assure public health safety in administration of antimicrobial preparations, etc. to meat or milk-producing animals, poultry, fish/crustacea or bees, to specify drugs that can be used, and their administration, dosages, and prohibition periods for use in the animals concerned.
### Example of Standards of Restriction for Usage of Veterinary Drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Target animal</th>
<th>Dosage</th>
<th>Prohibition period for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (in feed)</td>
<td>Cattle (not more than 6 months old)</td>
<td>- Administrate not more than 24 mg/kg bw/day</td>
<td>5 days before slaughter</td>
</tr>
<tr>
<td></td>
<td>Pigs</td>
<td>Administrate not more than 24 mg/kg bw/day</td>
<td>5 days before slaughter</td>
</tr>
<tr>
<td></td>
<td>Chickens</td>
<td>- Administrate not more than 40 mg/kg bw/day</td>
<td>2 days before slaughter</td>
</tr>
</tbody>
</table>

*Ampicillin level in beef should not exceed its MRL!*
Regulation of Veterinary drug Residues in Food

Marketing Approval System
- FSC : ADI (Risk assessment)
- MHLW : MRL
- MAFF : Withdrawal Period
  → Establishment of Appropriate Withdrawal Period

Distribution Control
- System for Drugs Requiring Veterinary Consultation
- Prescription System
  → Appropriate Use of Drugs under the veterinarian's control.

Use Control
- Restrictions on the Usage of Veterinary Drugs
  → These regulations will prevent the veterinary drug over MRL from remaining in food
Countermeasures against Antimicrobial Resistance (AMR)

Marketing Approval System
- FSC : Risk Assessment of AMR
- MAFF : Approval (included specifying method of administration, dose, precautions for use)

Distribution Control
- System for Drugs Requiring Veterinary Consultation
- Prescription System

Use Control
- Restrictions on the Usage of Veterinary Drugs

Other
- Second Choice Drug System
- Enlightenment of Prudent Use

→ These regulations will manage AMR
9. How many aquatic vaccines and herbal medicine have been licensed and permitted for using in Japan?

- **Herbal medicine**: about 50 products

How many batches you have to inspect aquatic vaccine and herbal medicine per year?

- **Herbal medicine**: about 0 products
  (once in several years)
Question items: appendix_2 drug part

1. Are there any specified test item in veterinary drugs need to done in registration? (in various dosage forms)

➢ See VICH GL39

“Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances”

(http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/pharma-specifications.html)
Question items: appendix_2 drug part

2. Does endotoxin test or particulate matter test need to perform in veterinary drugs injections?

➤ See VICH GL39

**Endotoxins/Pyrogens:** A test procedure and acceptance criterion for endotoxins, using a procedure such as the limulus amoebocyte lysate test, should be included in the specification in accordance with regional requirements. Pyrogenicity testing may be proposed as an alternative to endotoxin testing where justified.

**Japan**

injection and vehicles attached to preparations, other than those exclusively for intracutaneous, subcutaneous or intramuscular administration
(https://www.pmda.go.jp/files/000213750.pdf)

GENERAL RULES FOR PREPARATIONS


3. Preparations for Injection

3-1. Injections

(9) Unless otherwise specified, Injections and vehicles attached to preparations other than those used exclusively for intracutaneous, subcutaneous or intramuscular administration meet the requirements of Bacterial Endotoxins Test <4.01>. In the case where the Bacterial Endotoxins Test <4.01> is not applicable, Pyrogen Test <4.04> may be applied instead.
2. Does endotoxin test or particulate matter test need to perform in veterinary drugs injections?

- See VICH GL39

**Particulate matter:** Parenteral products should have appropriate acceptance criteria for particulate matter. This will normally include acceptance criteria for visible particulates and/or clarity of solution, as well as for sub-visible particulates as appropriate.

**Japan**

Unless otherwise specified, Injections and vehicles attached to preparations meet the requirements of Insoluble Particulate Matter Test for Injections
GENERAL RULES FOR PREPARATIONS


3. Preparations for Injection

3-1. Injections

(13) Unless otherwise specified, Injections and vehicles attached to preparations meet the requirements of the Foreign Insoluble Matter Test for Injections.

(14) Unless otherwise specified, Injections and vehicles attached to preparations meet the requirements of Insoluble Particulate Matter Test for Injections.
3. Can you provide animal drug regulations about unqualified products of control and punishment?

- Nobody can sell veterinary drugs without marketing approval.
- The user must observe “Standards governing restrictions on the usage of veterinary drugs used for food-producing animals”.
- Nobody can use anything other than veterinary drugs which have been already approved to food-producing animals.
- Punishment: Penal servitude three years or less, penalty that is less than 3 million yen or both.
Question items: appendix_2 drug part

4. Are there any aquatic animal drug or formulas had been approved especially for using in ornamental fish and food fish?

➢ See following site (food fish)

See following site (ornamental fish)

(http://www.nval.go.jp/asp/asp_dbDR_idx.asp)
Question items: appendix_2 drug part

5. Can you provide Japanese aquatic animal drug or formulas inspection standards about executing value effect, toxicological tests, and drugs residue tests etc. to us? And also, do testing fish type is object of host fish or other typical fish to do the tests?

- See VICH web site
  (http://www.vichsec.org/)

- NVAL Home Page
  (http://www.maff.go.jp/nval/hourei_tuuti/pdf/160805_betten2.pdf)
Question items: appendix_2 drug part

7. Are there any traditional medicine (like herbs or traditional Chinese medicine) already using in veterinary drugs?
   How about the regulation on registration, test item or reference?

➢ Yes
➢ As stated above
9. Is the disinfectant for farm used outlined in animal drugs or environmental drugs?

And, does this disinfectant used for specific virus (for instance AI, ND, FMD etc.) to do killing tests?

If you do, could you provide your testing references to us?

- The disinfectant for animal farm used is outlined in animal drugs.
- Usually No, if necessary Yes, but in vitro test only.
- We cannot provide you the data which were submitted by an applicant.
Thank you for your attention!!