Legal framework for the approval/designation of alternatives to antibiotics

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Topics

- National Action Plan on Antimicrobial Resistance (AMR) in Japan
- Approval of Veterinary Medicinal Products (VMPs)
- Designation of Feed Additives
- Promotion of R&D on Alternatives to antimicrobials
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• National Action Plan on Antimicrobial Resistance (AMR) in Japan
  • Approval of Veterinary Medicinal Products (VMPs)
  • Designation of Feed Additives
  • Promotion of R&D on Alternatives to antimicrobials
Adoption of AMR National Action Plan, April 5, 2016

Ministerial Council on the Response to Infectious Diseases that Pose a Threat to Global Society

Prime Minister Shinzo Abe:
- AMR is a global threat and Japan has determined our first action plan.
- We will advance effective measures for both humans and animals.
- Japan will lead the advancement of international measures such as by supporting the formulation of action plans in other countries.
- I request that all relevant ministers collaborate closely to steadily advance the relevant measures.
Japan’s national action plan

Japanese version

英語版

National Action Plan on Antimicrobial Resistance (AMR)

2016-2020

April 5, 2016
The Government of Japan
<table>
<thead>
<tr>
<th>Goal</th>
<th>Point of actions in animal sector</th>
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<tbody>
<tr>
<td>1. Awareness and education</td>
<td>• Raise awareness of stakeholders including livestock producers</td>
</tr>
<tr>
<td>2. Surveillance and monitoring</td>
<td>• Further promote collaboration between human health and animal health sectors</td>
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<td></td>
<td>• Expand the scope/target of monitoring and surveillance in aquaculture</td>
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<td>• Establish a monitoring and surveillance system for companion animals</td>
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<td>3. Infection prevention and control</td>
<td>• Ensure compliance of the Standards of Rearing Hygiene Management</td>
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<td>4. Appropriate use of antimicrobials</td>
<td>• Thoroughly implement risk management measures based on risk assessments</td>
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<td></td>
<td>• Further promote prudent use of antimicrobials</td>
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<tr>
<td>5. Research and development</td>
<td>• Promote R&amp;D of alternatives to antimicrobials including vaccines</td>
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<tr>
<td>6. International cooperation</td>
<td>• Contribution to the Asian Region</td>
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</tbody>
</table>
To promote
  1) fast approval of safe and efficacious VMPs;
  2) developments of VMPs for minor use/minor species;
  3) developments of products required for combatting AMR.

1. Developments of international harmonized technical guidelines
   VICH (International Cooperation on Harmonisation of Technical
   Requirements for Registration of Veterinary Medicinal Products)

2. Developments of national technical guidelines for products using
   new technology
   Support to develop national guidelines for brand new products

3. Developments of products using new technology
   Support to obtain data for dossier of products using new technology (e.g.,
   GMO vaccines) at the final stage of R&D (e.g., efficacy studies, safety
   studies, clinical trials)

4. Developments of products for minor use/minor species
   Support to obtain data for dossier of products for MUMS at the final stage
   of R&D (e.g., efficacy studies, safety studies, clinical trials)

5. Developments of products for combatting AMR
   Support to obtain data for dossier of products for combatting AMR (e.g.,
   Alternatives to antibiotics including vaccines) at the final stage of R&D
   (e.g., efficacy studies, safety studies, clinical trials)
Alternatives to antibiotics (ATAs)

- ATAs include, but are not limited to, vaccines, cytokines, enzymes, immunomodulators, immunostimulants, organic acids, probiotics, herbal medicines and bacteriophages.

The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Pharmaceuticals and Medical Devices Act)

Veterinary Medicinal Products (VMPs)

The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Pharmaceuticals and Medical Devices Act)

Feed additives

The Act on Safety Assurance and Quality Improvement of Feeds (Feed Safety Act)
Topics

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The Act for Ensuring the Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices (Act No.145, Series of 1960)

Enforcement ordinance (Cabinet ordinance No.11, Series of 1961)

Ministerial ordinance

Ministerial announcements

Regulatory rules for Veterinary Products (Ministerial ordinance No. 107, Series of 2004)
Restriction for the usage of VMPs and MPs (Ministerial ordinance No. 44, Series of 2013)
Ministerial Ordinances concerning GLP, GCP, GMP, etc.

Biological products standard, National testing standard, etc.

They cover veterinary medicinal products (VMPs) for all animal species

National/International (VICH) guidelines

Law hierarchy of Pharmaceutical Affairs in Japan

Notices
Article 1 (Purpose of the Act)

- The purpose of this Act is to improve health and hygiene by providing the control required for securing the quality, efficacy and safety of pharmaceuticals, quasi-pharmaceutical products, cosmetics, medical devices, regenerative medicine products (hereinafter referred to as "pharmaceuticals, etc.") and for preventing the occurrence or spread of health and hygiene-related hazards caused by the use of those pharmaceuticals, etc. by taking measures against designated substances, and by taking necessary measures for the promotion of research and development of pharmaceuticals, medical devices and regenerative medicine products which fulfill particularly high medical needs.

The same act regulates medicinal products for human use (MPs) and veterinary medicinal products (VMPs)
The term "pharmaceutical" used in this Act refers to the following items:

(i) items listed in the Japanese Pharmacopoeia;
(ii) items which are intended for use in the diagnosis, treatment or prevention of disease in humans or animals
(iii) items which are intended to affect the structure and functioning of a human or animal's body, and which are not medical appliances or instruments, etc.
PMD Act

Article 14 [Marketing Approval]

• A person who intends to market pharmaceuticals*¹, quasi-pharmaceutical products*² or cosmetics which contain components specified by the Minister must, for each product, obtain approval from the Minister with respect to its marketing.

*¹ Excluding pharmaceuticals with specified standards designated by the Minister
*² Excluding quasi-pharmaceutical products with specified standards designated by the Minister
Composition of dossiers (Vaccines)

[Application format]

Application for Marketing Approval

1. Name and address of manufacturer(s)
2. License No. of manufacturer(s)
3. Type of License
4. Name of the product
5. Ingredients and quantities
6. Manufacturing method
7. Administration and dosage
8. Label claim
9. Condition for storage
10. Shelf life
11. Quality control testing and acceptance criterion
12. References
Composition of dossiers (Vaccines)
[Appendixes (background study data)]

Appendix 1: Origin and background of development
Appendix 2: Physicochemical properties
Appendix 3: Production protocol
Appendix 5: Stability
Appendix 9: Target Animal Safety
Appendix 10: Efficacy
Appendix 14: Clinical trial
Appendix 1

The origin and background of the development

• Purpose of development
• Information on the target disease(s)
• Information on outbreaks of the target disease(s) in Japan
• Information on the similar products approved outside Japan
• Component comparison with similar vaccines already approved in Japan
Appendix 2

Physicochemical property of vaccine strain

• Origin of the strain and seed production process
• Attenuation, strain marker and stability (live vaccine)
• Excretion and cohabitation infection (live vaccine)
• Immunogenicity
• Absence of reversion to virulent form (VICH GL41)
• Safety of master seed in target animal
• Quality control testing (seeds, in-process and batch release) and acceptance criterion (VICH GLs)
Appendix 3

Protocol of production

Live-attenuated viral vaccine

1. Inoculate production seed virus in eggs

   Incubate for XXX days at 37 °C

2. Harvest, filter and centrifuge virus fluid

3. Dilute and add stabilizer

4. Place aliquots in vials and freeze-dry

Live-attenuated viral vaccine
Appendix 5

Stability of Final product (Shelf life)

• Method: Long-term stability test
• Sample: Final products
• Number of sample: 3 batches
• Test interval: every 3 (6, 12) months
• Test items: All items of the final products
Appendix 9

Target animal Safety test (TAS)

• GLP study
• Method: VICH GL44
• Material: final products
• Number of Animals: 8 animals in each group
• Administration dose:
  • Live vaccine given at 10 doses / animal
  • Inactivated vaccine given at 1 dose / animal
• Data Collection:
  • General clinical observations (vitality, diarrhea, respiration, body weight)
  • Injection site (histopathologically after euthanasia)
Appendix 10

**Efficacy**

- Minimum effective dose
- Minimum effective antibody titer
- Comparative study on sensitivity by age, breed and administration route
- Influence of maternal antibody on vaccination
- Duration of immunity
- Onset of immunity
Appendix 14

Clinical trial

• GCP study (VICH GL9)
• Objective:
  – To evaluate the efficacy and safety of the vaccine in the field
• Samples: Final products
• Number of test sites: More than 2 sites
• Number of Animals:
  – ≥ 200 chickens
  – ≥ 60 head for mammals
• Test period:
  – Adequate period for evaluation of safety and efficacy of the vaccine in field
## Composition of dossiers (Chemicals)

### [Application format]

<table>
<thead>
<tr>
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<tr>
<td>1</td>
<td>Name and address of manufacturer(s)</td>
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<td>5</td>
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<td>7</td>
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<td>Shelf life</td>
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Composition of dossiers (Chemicals)

[Appendixes (Background study data)]

App. 1: Origin and background of the discovery
App. 2: Physicochemical properties
App. 3: Production protocol
App. 5: Stability
App. 6: Toxicity (acute toxicity)
App. 7: Toxicity (sub acute and chronic toxicity)
App. 8: Toxicity (special toxicity (e.g. mutagenicity, local irritation, etc.))

* App. 4 is only for Medical Devices
Composition of dossiers (Chemicals)
[Appendixes (Background study data)]

App. 9: Target Animal Safety
App.10: Pharmacology related to efficacy
App.11: General pharmacology
App.12: ADME (absorption, distribution, metabolism and excretion)
App.14: Clinical trial
App.15: Residue for food producing animals

* App. 13 is only for Medical Devices
Appendix 5

**Stability**

- **Active ingredient**
  Guideline: *VICH GL3R*
  - Long term
  - Accelerated
  - Photostability (*VICH GL5*)

- **Final product**
  Guideline: *VICH GL3R*
  - Long term
  - Accelerated
  - Photostability (*VICH GL5*)

- **Other GLs** (*VICH GL4, GL8, GL17, GL45, GL51*)
Appendix 6-8

**Toxicity**

- General approach to testing ([VICH GL33](#))
- Acute toxicity
- Sub acute and chronic toxicity ([VICH GL31, GL37](#))
- Reproduction toxicity ([VICH GL22](#))
- Developmental toxicity ([VICH GL32](#))
- Genotoxicity ([VICH GL23](#))
- Additional studies if needed
Appendix 10

Efficacy

• Mode of action
• Minimum effective dose
• Basis of administration route and dosage
Appendix 11

General pharmacology

Effects for

- central nervous system,
- autonomic nervous system,
- respiratory system,
- circulatory system and
- gastrointestinal system
Appendix 14

**Clinical trial**

- **Objective:**
  - To evaluate the efficacy and safety of the final product in the field

- **Samples:** Final product

- **Number of test sites:** More than 2 sites

- **Number of Animals:**
  - ≥ 200 chickens
  - ≥ 60 head for mammals

- **Test period:**
  - Adequate period for evaluation of efficacy and safety
Appendix 15

Residue for food producing animal

• Objective:
  – To evaluate the residue of active ingredient in the food producing animals when the veterinary drug product administrates with maximum dose and maximum period. This study will be used for establishing of MRL and withdrawal period.

• Methods: VICH GLs 46-49
Article 14, paragraph 8

When any one of the following items is met, the Minister shall seek the opinion of Pharmaceutical Affairs and Food Sanitation Council (PAFSC) before granting the approval specified in Paragraph 1.

1. The expert of veterinary medicine, pharmaceutical sciences, toxicology, bacteriology, etc.

Drugs for food producing animals

1. Drug residues
   - PAFSC

2. Human health safety
   - Food Safety Commission of Cabinet Office (FSC)
From application to approval

- Application
- MAFF
- Pharmaceutical Affairs and Food Sanitation Council (Review for approval)
- The Food Safety Commission (Setting of ADI)
- Ministry of Health, Labour and Welfare (Setting of MRL)
- Approval
Topics

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Feed Additives

Feed additives in Feed Safety Act refer to:

- those used in feeds by adding, mixing, infiltrating, etc.
- for the purpose specified by MAFF Ordinance,
- which are designated by the Minister of Agriculture, Forestry and Fisheries after consultation with the Agricultural Materials Council.

**Purposes specified by MAFF Ordinance**
- Prevent deterioration of feed quality
- Supply of nutrient ingredients and other effective ingredients of feed
- Promote efficient use of feed nutrient ingredients
Procedure for designating feed additives

MAFF

Agricultural Materials Council
Risk assessment of feed
(Effect and safety to animals, etc.)
Draft specifications of the feed additives
Evaluation of public comments
Final specifications

Seek opinion

Request for risk assessment of feed

Ministry of Health, Labour and Welfare

Request for risk assessment of food

Food Safety Commission
Risk assessment of food and feed
(in terms of food safety of animal products from animals fed with the feed)
Draft of assessment report of food and feed
Evaluation of public comments
Final assessment report

Report to MAFF

Designating the feed additives
Setting the specifications
Assessment standards for feed additives

1. Efficacy
2. Residue
3. Safety

of candidate feed additives are discussed at the Agricultural Materials Council
Approval/designation Procedure

Assess efficacy, safety and residue for animals

Assess residue in food

Assess safety for human

includes AMR risk assessment

VMPs

Feed Additives

PAFSC

AMC

Ministry of Health, Labour and Welfare

Food Safety Commission

MAFF

Approval

Designation
Topics

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• Approval of Veterinary Medicinal Products (VMPs)

• Designation of Feed Additives

• Promotion of R&D on Alternatives to antimicrobials
VMPs are essential tools for comprehensive control of the animal diseases. Feed additives are important for the production of healthy animals. Our Industry highly contributes to animal health worldwide.

Our mission as the Regulatory Authority is to provide safe and efficacious products with high quality to veterinarians, farmers and pet owners as early as possible. To achieve this, we continue to improve our approval/designation process for VMPs and feed additives.

Japan promotes the developments of alternatives to antibiotics by financially supporting the final stage of the developments.
For the promotion of R&D

- Technical guidelines are fundamental for research & development by applicants and review by regulatory authority. Japan promotes to develop new national and international guidelines for VMPs with close relationship with Industry/Academia.

- Fast Track Approval for VMPs to be used for combatting AMR is under consideration. (Congress passed the bill on amendment of Pharmaceuticals and Medical Devices Act in November)

- To maintain communications between Regulatory authorities and Industry (as partners) is the key for the fast development and approval of the products; thus, for the future of animal and public health.
Thank you very much for your attention!!