For Promoting "Responsible & Prudent Use" of Veterinary Antimicrobials

Prudent use

Antimicrobials / Antibiotics

Resistant bacteria

Risk Reduction of Antimicrobial Resistant (AMR) Bacteria

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Animal Products Safety Division
Food Safety and Consumer Affairs Bureau,
Ministry of Agriculture, Forestry, and Fisheries
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Introduction

Veterinary antimicrobial medical products (hereinafter, “antimicrobials”) are important materials to protect the health of livestock and to ensure the stable production supply of safe food. On the other hand, their use always involves a risk of selecting antimicrobial resistance bacteria that might bring adverse effects to human medicine and veterinary medicine.

For this reason, the Ministry of Agriculture, Forestry and Fisheries (MAFF) promotes the appropriate use of antimicrobials as well as takes measures for risk management based on the results of risk assessment conducted by the Food Safety Commission of Japan (FSC) regarding the impact on human health through foods with AMR.

To reduce any risks of AMR, role of every veterinarian who actually selects and uses antimicrobials/ antibiotics in the field is important.

Given these understandings, we have developed the basic concept of thorough implementation of responsible and prudent use of antimicrobials in the field of livestock production.

(*) Notification on December 24, 2013, “Basic Concept of Prudent Use of Veterinary Antimicrobial Agents for Animals in the Field of Livestock Production".

This booklet summarizes the necessary basic information and inspection methods for carrying out this concept. We would greatly appreciate your utilization of this booklet and for your understanding and cooperation in the prudent use of antimicrobials.
Antimicrobial resistance (AMR) should be addressed by close collaboration among veterinarians, producers, administrators, etc. The Ministry of Agriculture, Forestry and Fisheries takes risk management measures based on assessments by the Food Safety Commission of Japan. The roles of veterinarians and producers are significant in ensuring the effectiveness of risk management measures.

Overview of Prudent Use of Veterinary Antimicrobial Medical Products in Livestock Production

**Background**
- Contain as far as possible the selection and transmission of antimicrobial resistant bacteria among livestock
- Prevent the livestock-to-human transmission of antimicrobial resistant bacteria or antimicrobial resistant determinants, and maintain effectiveness of antimicrobials used in humans
- Maintain effectiveness of antimicrobials used in livestock

**Prudent Use of Antimicrobials**

1. **Preventing infections by appropriate rearing hygiene management**
   - Preventing outbreaks of infections is very important elements for controlling antimicrobial resistant bacteria.
   - Maintenance of health by appropriate rearing environment and prevention of infections by vaccination

2. **Appropriate Understanding and Diagnosis of Diseases**
   - Obtaining epidemiological information such as history of past infection outbreaks.
   - Determination of a treatment plan after identifying the causative bacteria by diagnosis by a veterinarian.

3. **Selection and use of Antimicrobials**
   - Selecting the effective antimicrobials based on antimicrobial susceptibility testing
   - Second-line antimicrobials such as fluoroquinolones should only be chosen when the first-line antimicrobial is ineffective.
   - Use of unapproved medicines and off-label use shall not be allowed as a general rule.
   - Evaluate effectiveness after administration, and change antimicrobials as necessary.

4. **Sharing information among parties involved**
   - Sharing the information with all stakeholders on the outbreaks of antimicrobial resistant bacteria and distribution of antimicrobials.
**What are "Antimicrobial Resistant Bacteria"?**

**It refers to the bacteria that can grow even under the existence of antimicrobials**

- Bacteria generate its own resistance mechanism (mutation of a chromosome, etc.) and acquire a resistance genes which antibiotic producing microorganism or antimicrobial resistant bacteria have (Transmission of resistance).
  - Mutation: Alteration of chromosomal genes in the process of bacterial growth.
  - Transmission of resistance: Intercellular exchange of genes resistant to antimicrobials. Examples of resistance genes: plasmid, transposon, integron, phage. etc.
- Acquisition of resistance genes is occurring with a certain probability, and it does not depend on the presence of antimicrobial.
- However, comparing with susceptible bacteria, antimicrobial resistant bacteria can grow advantageously in the presence of antimicrobial. Such a phenomenon, where antimicrobial resistant bacteria survive and grow while susceptible ones cannot grow, is referred to as the “selection of antimicrobial resistant bacteria”.

**AMR mechanism of bacteria**

- **Antimicrobials**
- **Decrease of permeability**
- **Inactivation of antimicrobials**
- **β-lactam, Aminoglycoside**
- **Chromosome**
- **Cytoplasm**
- **Cytoplasmic membrane**
- **Outer membrane**
- **Excretion of antibacterials (Efflux mechanism)**
- **Quinolone Macrolide**
- **Alteration in point of action**

- Inactivated enzymes
Criteria of antimicrobial resistance

Minimum Inhibitory Concentration (MIC) for the bacteria, which is determined in antibiotic susceptibility test, determines whether it is AMR bacteria.

MIC: Minimum Inhibitory Concentration
Minimum concentration of a antimicrobial needed to inhibit the growth of bacteria

Bacteria with MIC that has exceeded a break point (resistance limit value: BP)

Antimicrobial resistant bacteria

Eg: If the BP of Antimicrobial A is 1 μg/mL, a bacterial strain with MIC of 0.5 μg/mL is considered a sensitive bacterium, while one with MIC of 2 μg/mL is considered an antimicrobial resistant bacterium.

BPs are set by the standards described below, with some general ones determined by the Clinical and Laboratory Standards Institute (CLSI, US) and other institutions.

Setting of break points

- **Microbiological Break Point**
  The intermediate value of each peak value when it shows that the distribution of MIC is more than a binominal distribution, because the MIC shows a normal distribution

- **Clinical Break Point**
  Boundary point at which therapeutic effect can be expected clinically after administering antimicrobials to diseased livestock

(e.g.) BPs are subject to change depending on the antimicrobial used and infection concerned due to the influence of the pharmacokinetics of the antimicrobial etc. An example is shown below.

![Diagram of Microbiological BP and Clinical BP](attachment:diagram.png)
What is "appropriate use of antimicrobials"?

The use of antimicrobials in compliance with laws and regulations concerning dosage, administration, and indications, as well as precautions.

- Systems for the appropriate use of antimicrobials
  - Selling Prescription Pharmaceuticals (Article 49, the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices)
    - Selling based on instruction by a veterinarian
  - Restrictions on use (Article 83-4, Article 82-5 the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices)
    - Compliance obligation according to dosage, administration and withdrawal period
  - Issuing of Pharmaceuticals Requires Medical Examination (Article 18, Veterinary License Act)
    - Obligation that a veterinarian need to examine an animal before administering antimicrobials or issuing instructions

- Risk of antimicrobial resistant bacteria

  There is a case that antimicrobials administered to livestock hardly have an effect depending on the selected antimicrobial resistant bacteria.

  In addition, when AMR bacteria are transmitted to humans through foods, there may be a possibility that antimicrobial used in treatment for humans does not work sufficiently.

- Risk Assessment of Antimicrobials/ Antibiotics

  The Food Safety Commission of Japan assesses the impact which AMR bacteria selected by the use of antimicrobials affect human health through foods.

- Risk Management of Antimicrobials

  The Ministry of Agriculture, Forestry and Fisheries is promoting the appropriate use of antimicrobials (*1), and at the same time is taking risk management measures (*2) based on the Guidelines for Establishing Risk Management Measures for Veterinary Antimicrobial Agents in response to the results of risk assessment by the Food Safety Commission.

(*1) What is "appropriate use of antimicrobials"?
The use of antimicrobials in compliance with laws and regulations concerning dosage, administration, and indications, as well as precautions.

(*2) Examples of measures for risk management
The Risk management measures taken against the antimicrobials that have been assessed as having medium risk
  - Strictly to be used as a second-line drug
  - Enhancing the monitoring of AMR bacteria conducted by the Ministry of Agriculture, Forestry and Fisheries
  - Enhancing the monitoring of AMR bacteria conducted by manufacturers and distributors
The antimicrobial used as the sole medicine for treatment of a specific human disease, or few alternative antimicrobials are available. Eg: Fluoroquinolones, third generation cephalosporins, etc.

I: Critically important

The antimicrobial used as the sole medicine for treatment of a specific human disease, or few alternative antimicrobials are available. Eg: Fluoroquinolones, third generation cephalosporins, etc.

II: Highly important

For treatment of human infectious diseases caused by the antimicrobial resistant bacteria, alternative antimicrobials are available, but the number of the alternatives is extremely limited compared with that for antimicrobials ranked as III. Eg: Streptomycins, lincomycins, etc.

III: Important

For treatment of human infectious diseases caused by antimicrobial resistant bacteria, alternative antimicrobials are available sufficiently among the same or different classes of antimicrobial. Eg: Sulfonamides, Old quinolones, etc.
In accordance with this guideline, risk management measures are formulated to ensure the food safety and efficacy of antimicrobials for livestock. Specifically, measures are selected from the list of feasible risk management measures (Table 1) on the basis of the results of the Food Safety Committee’s risk assessment (Table 2) and the factors for decision making (Table 3).

**Table 1: Feasible Risk Management Measures**

<table>
<thead>
<tr>
<th>Risk management measure</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revocation of approval to manufacture and sales</td>
<td>The concerned antimicrobials is discontinued to be distributed and used.</td>
</tr>
<tr>
<td>Provisional prohibition of use</td>
<td>The concerned antimicrobials shall be prohibited from being distributed (may not be used) within Japan for a certain period (assumed to be for a few years).</td>
</tr>
<tr>
<td>Deletion of dosage forms</td>
<td>If the antimicrobial is approved for two or more dosage forms, some of such forms shall not be used.</td>
</tr>
<tr>
<td>Deletion of targeted livestock and aquatic animals</td>
<td>If the antimicrobial is approved for two or more animal species, some of the species shall be deleted from the targeted livestock. Such species may be examined separately for each dosage form.</td>
</tr>
<tr>
<td>Deletion of indications/applicable bacterial species</td>
<td>If the antimicrobial is approved for a number of indications/applicable bacterial species, some of them shall be deleted. Such indications/applicable bacterial species may be examined depending on the dosage form.</td>
</tr>
<tr>
<td>Restriction of use in the latter half of feeding period</td>
<td>Restricting use during the latter half of feeding period, when larger amount of antimicrobials is needed per individual animal, shall reduce the total administration amount. This shall also contain the increase of resistant bacteria before shipping, caused by selectivity pressure due to use in latter feeding period.</td>
</tr>
<tr>
<td>Shortening of the administration period</td>
<td>Amount of administration per individual animal shall be reduced by shortening of the administration period.</td>
</tr>
<tr>
<td>Thorough implementation as a second-line drug</td>
<td>This is indicated in the precautions of New quinolone antimicrobials or 3rd to latest generation cephalosporin. This requirement shall restrict antimicrobials from being used for cases where the first-line medicine is ineffective.</td>
</tr>
<tr>
<td>Strengthening of monitoring</td>
<td>Increasing monitoring frequency and data points shall contribute to prompt detection of development of resistance.</td>
</tr>
<tr>
<td>Others</td>
<td>Risk management measures shall be considered as necessary, corresponding to the features of the antimicrobials.</td>
</tr>
</tbody>
</table>

**Table 2: Perspectives for risk management measures for each risk estimate division**

<table>
<thead>
<tr>
<th>Risk management policy</th>
<th>Category</th>
<th>Examples of risk management measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strengthen risk management measure</td>
<td>High</td>
<td>Revocation of approval, Provisional prohibition of use, Deletion of dosage forms, Deletion of targeted livestock and aquatic animals</td>
</tr>
<tr>
<td>Medium</td>
<td>Deletion of indications/applicable bacterial species, Restriction of use in the latter half of feeding period, Shortening of the administration period, Thorough implementation of the use as a second-line drug, Strengthening of monitoring</td>
<td></td>
</tr>
<tr>
<td>Continue risk management measure</td>
<td>Low</td>
<td>Negligible</td>
</tr>
<tr>
<td>Continue monitoring</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Factors for decision making when selecting risk management measures**

<table>
<thead>
<tr>
<th>Factors for decision making</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Importance of antimicrobials on veterinary medicine</td>
<td>Severity of disease treated by concerned antimicrobials (e.g. spread of disease and disease state) and significance of antimicrobials for clinical veterinarians (e.g. usability, efficacy and cost)</td>
</tr>
<tr>
<td>Existence of alternatives and alternative measures</td>
<td>Existence of other antimicrobial agents clinically equivalent to concerned antimicrobial agents, Existence of alternative measures such as vaccine</td>
</tr>
<tr>
<td>Secondary risks</td>
<td>Probability and level of spread of diseases in livestock and aquatic animals and increase of pathogenic bacteria, bacteria causing food-borne disease and antimicrobial resistant bacteria if risk management measures are enforced</td>
</tr>
<tr>
<td>Effect of reducing risk</td>
<td>Expected level of reducing risk of selecting antimicrobial resistant bacteria if risk management measures are enforced</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Feasibility of risk management measures in terms of technical, administrative and financial aspects</td>
</tr>
<tr>
<td>Others</td>
<td>Any factors which should be considered because of characteristics of concerned antimicrobial agents</td>
</tr>
</tbody>
</table>
“Prudent use” shall mean usage, after a thorough examination of the appropriateness of such usage, aimed both at maximizing the efficacy of antimicrobials by appropriate use and containing selection of antimicrobial resistant bacteria as far as possible.

To reduce the risks of antimicrobial resistant bacteria selected by the use of antimicrobials, relevant parties including veterinarians are required to cooperate with each other to encourage responsible and prudent use.

### Goal

- **Suppress the selection and transmission of antimicrobial-resistant bacteria in livestock.**
  - Maintain the effectiveness of antimicrobials in livestock
  - Maintain the effectiveness of antimicrobials for human use by suppressing the transmission of antimicrobial-resistant bacteria to humans.

#### Critically important antimicrobials for human medicine:
- Fluoroquinolones and third generation cephalosporins, etc.

### Prudent use

**Appropriate use**
- Required instruction
- Compliance with laws and regulations
- Use Standard
- Others

**Others**
- Implementation of antimicrobial susceptibility test
- Prevention of infection
- Selection of appropriate antimicrobials
- Sharing the information related to antimicrobials
Decrease the use frequency of antimicrobials by maintaining the health of livestock and preventing infection.

**Suppressing the selection of antimicrobial resistant bacteria**

The following measures are necessary to prevent infection:

- Improvement of rearing environment adversely affecting the health state of livestock
- Appropriate vaccination
- Appropriate feeding and nutritional management
- Compliance with the Standards of Rearing Hygiene Management (*)

(*) For the details of the hygiene management methods, please refer to the "Standards of Rearing Hygiene Management" issued by the Ministry of Agriculture, Forestry and Fisheries.

- The Ministry has also compiled and published the “Production Hygiene Management Handbook (beef cattle, broiler and layer chickens)” describing a set of measures that producers are requested to take to improve food safety. Please make use of it as well.

- Ensure that the above measures are properly implemented on a regular basis, and in case of a problem, instruct the producer on good practices.
- Share information on the use of antimicrobials among the parties concerned.

**Sharing information among parties Concerned**

- Outbreaks of infection
- Usage of Antimicrobials
- Information on prevention/treatment of infections
- Precautions for use of antimicrobials
Treatment with antimicrobials should be performed based on the results of bacterial isolation and antimicrobial susceptibility testing.

In case of an infection outbreak, understand the characteristics of the disease and make appropriate diagnosis while keeping the below points in mind:

- Interview the producer on the progress and measures taken after the outbreak, and assess the pathogen and pathology through clinical pathological examination etc.
- Keep tabs on the epidemiological information.
- Isolate bacteria to search for the causative strain.
- Perform susceptibility testing on the isolated causative strain.

Selection of antimicrobials

- Select effective antimicrobials based on the results of antimicrobial susceptibility testing.
- Select a drug with the narrowest possible antimicrobial spectrum as the first-line drug among those that have shown effectiveness to causative bacteria in the antimicrobial susceptibility testing.
- Fluoroquinolones etc. are restricted for use as the second-line drugs. (*)

(*) The antimicrobials to be approved as the second-line drugs for livestock (as of December 2013):
- Fluoroquinolones (enrofloxacin, ofloxacin, norfloxacin, orbifloxacin, marbofloxacin, danofloxacin, difloxacin)
- Third generation cephalosporins (ceftiofur, cefquinome)
- 15-membered ring macrolide (tulathromycin)

For the latest lists, please visit the National Veterinary Assay Laboratory’s website (URL: http://www.maff.go.jp/nval/yakuzai/pdf/h301030_fluoroquinolone.pdf)

Use of antimicrobials

- Use on the basis of the approved dosage, administration, indications and use standards.
- In principle, do not use unapproved drugs or prescribe for off-label indications.

After the use of antimicrobials

- Perform post-administration effect evaluation, and change antimicrobials as necessary.
Sampling

Smear the sample so that colonies can form on DHL agar medium (isolation culture)

Incubate at 37 °C for 18-24 hours

Confirm colonies of presumed E. coli (purplish red colonies on DHL).

Note: Smear the sample directly to DHL plate with an inoculation loop or microstreaker so that colonies can form.

* Smearing example

(Isolation)  
Implement as needed
The following method is an example:

Subject the above presumed E. coli colonies to pure culture on normal agar.

<table>
<thead>
<tr>
<th>Characteristics test</th>
<th>Test items</th>
<th>Simple preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>What to use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSI medium</td>
<td>Resolution</td>
<td>Y/Y</td>
</tr>
<tr>
<td></td>
<td>Hydrogen sulfide production</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Gas production</td>
<td>+ or –</td>
</tr>
<tr>
<td>LIM medium</td>
<td>Lysine decarboxylation</td>
<td>+ or –</td>
</tr>
<tr>
<td></td>
<td>Indole production</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Motility</td>
<td>+ or –</td>
</tr>
<tr>
<td>Cytochrome disc</td>
<td>Oxidase production</td>
<td>–</td>
</tr>
</tbody>
</table>

Api 20E (if ID% is equal to or more than 80%, it is considered to be E.coli)

- DHL (Desoxycholate-hydrogen sulfide-lactose) medium: isolation medium for selecting enterobacteria
- TSI (Triple Sugar Iron) medium: culture for differentiating enterobacteria
- LIM (Lysine Indole Motility) medium: medium: medium for differentiating enterobacteria
- Api 20E: Biochemistry test kit for identifying bacteria
Diffusion Methods

**Disc Diffusion Method**: Measures the diameters of inhibition zones by using disks containing a certain concentration of the antimicrobial.

**Gradient Diffusion Strip**: Measures the MIC by using a strip with stable gradient of antimicrobial concentrations.

Dilution methods

**Agar Dilution Method**: Measures the MIC by using agar plates with serial concentrations of the antimicrobial.

**Broth microdilution method**: Measures the MIC by using 96-well microplates containing liquid medium with serial concentrations of the antimicrobial.

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Note: The following institutions have published the standard protocols of each method.

- Clinical and Laboratory Standards Institute (CLSI, US)
- European Committee on Antimicrobial Susceptibility Testing (EUCAST)
- Japan Society of Chemotherapy
Disk method

Extract the test strain from non-selective agar medium and suspend it in physiological saline etc.

Alternatively

Inoculate the test strain into TSB medium, incubate for 2-6 hours, and then adjust the concentration of the bacterial solution with physiological saline etc.

* In either case, the solution should be adjusted to McFarland 0.5 with turbidity standard solution.

Smear evenly the prepared bacterial solution on Mueller-Hinton agar medium with a sterile cotton swab.

Let the smeared agar medium rest for 3-5 minutes.

Place the disks on the agar medium.

Incubate the bacteria by strain.

Evaluation

Disk

Note: Leave at least 24 mm of space between disks.

Diameter of an inhibition zone

Note: Measure the diameter of an inhibition zone completely inhibiting bacterial growth with a vernier caliper in the unit of mm. Resistance is judged based on the diameter.

- TSB (Trypticase Soy Broth) medium: A growth medium for bacteria with less strict nutritional requirements.
- McFarland turbidity standard solution: A standard solution for adjusting the concentration of bacterial suspensions. The concentration is estimated by comparison with the turbidity of the standard solution.
The method for identifying MIC by the size of the inhibit band.
Dispense the bacterial suspension to each well.

Adjust turbidity of the test strains incubated overnight with sterile physiological saline to Mcfarland 1.

Add the suspension solution to Mueller-Hinton broth etc. and mix it.

Prepare a 2-fold serial dilution series of the antimicrobial.

Dispense the liquid medium containing each antimicrobial to each well.

Incubate at 35 °C for 16-20 hours.

Determine the MIC from the growth of bacteria at each concentration.

Note: This flowchart only describes the most general protocol for reference. When conducting an actual experiment, please refer to the standard protocols provided by the CLSI, EUCAST and Japanese Society of Chemotherapy etc.

Dry/frozen plates with pre-adhered antimicrobials at different concentrations are commercially available.

The negative results at 8, 16 and 32 μg/ml indicate that the minimum concentration of 8 μg/ml is the MIC.

Lack of bacterial growth produced no turbidity = Negative (-)

Bacterial growth produced white turbidity = Positive (+)
**Determination criteria for positivity (+)**
- When macroscopic observation detects a pellet measuring 1 mm or more in diameter.
- When 2 or more pellets are observed even if their diameter is less than 1 mm.

**Determination criteria for negativity (-)**
- When macroscopic observation detects neither turbidity nor pellet.
- When, if any, there is only one pellet measuring less than 1 mm in diameter.

In the picture to the left, red circles signify the MIC values.
Agar dilution method

Incubate the test bacterial strains and quality control strains into non-selective medium (e.g., normal agar medium) so that colonies can form.

- Incubate at 35 °C for 18-24 hours

Inoculate the strains incubated in agar medium into TSB medium (4 ml).

- Incubate at 35 °C for 18-24 hours

Preparation of antimicrobials
Prepare a 2-fold serial dilution series of the antimicrobial.

<table>
<thead>
<tr>
<th>Antimicrobial Concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1280</td>
</tr>
</tbody>
</table>

Preparation of the medium
Prepare the medium by mixing 2 ml of the above diluted solutions and 18 ml of Mueller-Hinton agar medium.

Inoculate the prepared bacterial suspensions onto plate using a specialized tool.

Evaluation

- Incubate at 35 °C for 18-24 hours

Antimicrobial concentration

<table>
<thead>
<tr>
<th>Antimicrobial concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>128</td>
</tr>
</tbody>
</table>

Inoculate with the bacterial suspensions

Bacterial colony

MIC
A: >128 μg/ml  B: 128 μg/ml  C: 64 μg/ml

Note: This flowchart only describes the most general protocol for reference. When conducting an actual experiment, please refer to the standard protocols provided by the CLSI, EUCAST and Japanese Society of Chemotherapy etc.
Dilution/preparation of bacterial suspension

Prepare several bacterial suspensions when examining multiple antimicrobials with the same strain group. Exchange to a new batch for inoculation after testing for five antimicrobials.

Arrangement of bacterial strains

Quality control strains (4 strains)

Test strains

Evaluation of results

Colonies with macroscopically observable bacteria that appear to be bulging.

Evaluation: +

[View from above] [View from side]

Colonies with macroscopically unobservable bacteria, or those with observable but not bulging (membranous) bacteria.

Evaluation: -

[View from above] [View from side]

Antimicrobial concentration

The higher the antimicrobial concentration of the medium, the fewer bacteria can grow.
### Applicable page | Name of Journal
--- | ---

| | Alan R. Hauser (translated by Kentaro Iwata); “Antibiotics Basics for Clinicians” Medical Sciences International (2008) |
| | MAFF, National Veterinary Assay Laboratory; “Survey of Antimicrobial susceptibility of bacteria from livestock animal origin” http://www.maff.go.jp/nval/tyosa_kenkyu/taiseiki/ |
| | MAFF, Management Improvement Bureau; “Guidelines for Use of Antimicrobial Agents in Livestock Mutual Aid” http://www.maff.go.jp/j/keiei/hoken/saigai_hosyo/s_yoko/ |
| (P12-) | Japanese Society of Chemotherapy; Committee report & Guidelines List http://www.chemotherapy.or.jp/guideline/ |
| | European Committee on Antimicrobial Susceptibility Testing; Antimicrobial Susceptibility testing http://www.eucast.org/antimicrobial_susceptibility_testing/ |
| (P13, 14) | Pharmaceuticals and Medical Devices Agency; KB Disk® “Eiken”, the Homepage providing Pharmaceutical Medical Device Information http://www.info.pmda.go.jp/tgo/pack/09A2X10001000010_A_02_04/ |
| (P14) | Pharmaceuticals and Medical Devices Agency; Etest® Form Pack for Antibiotic Sensitivity Test, the Homepage of providing the Pharmaceutical Medical Device Information http://www.info.pmda.go.jp/tgo/pack/13A2X00243000039_A_01_01/13A2X00243000039_A_01_01?view=body |