Basic Concept of
Prudent Use of Veterinary Antimicrobial Agents
for Animals in the Field of Livestock Production

Introduction

Veterinary antimicrobial medicinal 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.

Therefore, the Food Safety Commission of Japan (FSC) has been evaluating the risks concerning the impacts of antimicrobial resistant bacteria on human health through foods, and the Ministry of Agriculture, Forestry, and Fisheries (MAFF) has been implementing risk management measures such as strengthened monitoring, based on risk assessment conducted by FSC.

International organizations such as the World Organization for Animal Health (OIE) and Codex, and many other nations have developed guidelines for the use of antimicrobials. “Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine” in OIE Terrestrial Animal Health Code, declares that all stakeholders, including regulatory authorities relating to use of antimicrobials in the course of producing livestock products; manufacturers and wholesalers of antimicrobials; retailers; veterinarians; and stock farm producers, should make efforts to carry out their action responsibly, to promote such “responsible and prudent use”. The Codex provides “Code of Practice to Minimize and Contain Antimicrobial Resistance” and other guidelines to promote such responsible and prudent use.

Japan has also attempted to promote appropriate use of antimicrobials by prohibiting sales of them without prescription, establishing standards for antimicrobial usage or other measures, based on the Pharmaceutical Affairs Act (the present Act on Securement of Quality, Effectiveness, and Safety of Pharmaceuticals and Medical Devices (Act No. 145 of 1960)). To further reduce the risk of antimicrobial resistant bacteria selected through use of antimicrobials, all stakeholders should make efforts to coordinate actions for

responsible and prudent use, and for this achievement the role of veterinarians and producers administering the antimicrobials is significantly 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.

Ⅰ. Basic Policy

Basic policies for responsible and prudent use of antimicrobials in livestock production are as follows:

1. To contain as far as possible the selection and spread of antimicrobial resistant bacteria in livestock production
2. To contain the spread of antimicrobial resistant bacteria or antimicrobial resistant determinants from livestock to human, and to maintain effectiveness of antimicrobial agents used in humans
3. To maintain effectiveness of antimicrobials used in livestock production

Ⅱ. Definition of Terms

The definitions of the terms used in this document shall be as follows:

1. “Antimicrobials” shall mean antibiotic and/or synthetic antibacterial agents that inhibit growth or kill microorganisms, by selectively acting on particular sites of metabolic or growth mechanisms of such microorganisms
2. “Antimicrobial resistant bacteria” shall mean bacteria that have acquired the ability to resist antimicrobial agents by genetic mutation or getting antimicrobial resistance genes (for example, Plasmid-mediated antimicrobial-resistance genes may be transferred antimicrobial resistance to other bacteria)
3. “Appropriate use” shall mean usage compliance to laws and ordinances, dosage and administration, and precautions
4. “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
5. “Off-label use” shall mean usage not following the dosage and administration or the indications that are approved as veterinary medicinal products and notified on the labels

Ⅲ. Outline of Antimicrobials and Antimicrobial Resistant Bacteria

1. Antimicrobials act on bacteria selectively. Mechanisms of such actions

include, cell wall synthesis inhibition (e.g. penicillin), protein synthesis inhibition (e.g. aminoglycoside, tetracycline, and macrolide), nucleic acid synthesis inhibition (e.g. quinolone) coenzyme inhibition (e.g. sulphonamide), and cell membrane inhibition (e.g. colistin).

2. Among the wide varieties of bacterial populations in the ecosystem, use of antimicrobial agents may encourage certain resistant bacteria to grow and propagate more actively, compared with bacteria that are sensitive to such antimicrobial agents. This process of growth/ propagation of resistant bacteria and the extermination of sensitive bacteria are known as "selection of antimicrobial resistant bacteria".
3. Antimicrobial resistant bacteria are the various bacteria existing in the natural environment that have antimicrobial resistant mechanisms. Some antimicrobial resistant determinants of such resistant bacteria spread to other bacteria through conjunction (plasmid), transduction (phage), transposition (transposon), or transformation.
4. To implement responsible and prudent use of antimicrobials based on scientific evidence, we must be familiar with depth the features, pharmacokinetics, and action mechanisms of each of antibiotics, as well as the mechanism for emergence and spread of antimicrobial resistant bacteria, its genetic mechanism, epidemiology and more. We shall not explain in detail the above matters in this document, but shall introduce some main books and references later in Chapter V.

Ⅳ. Basic concept of responsible and prudent use of antimicrobials in livestock production

1. Preventing infections by appropriate rearing hygiene management

Enhancing the rearing hygiene management level, keeping the livestock animals in healthy condition, and preventing outbreaks of infections all contribute to fewer opportunities for using antibiotics, and are very important elements for containing selection of antimicrobial resistant bacteria. For this reason, the owner of livestock animal should make efforts to comply in depth to the rearing hygiene management standards prescribed in Act on Domestic Animal Infectious Diseases Control (Act No. 166 of 1951), as well as deal with

matters set forth below to prevent infections:

(1) Improve rearing environment that causes adverse effect for livestock health conditions (e.g. high/low temperature and/or humidity within the shed, or bad ventilation)

(2) Appropriate vaccination to prevent infections

(3) Appropriate feeding and nutrition management to maintain health condition of the livestock animals

The veterinarians shall regularly check for compliance with the rearing hygiene management standards and matters (1)-(3) above, taking into consideration the characteristics and conditions of the animals, and in cases of any trouble arising, shall instruct the owner or manager of the animals to solve the problem.

2. Appropriate understanding and diagnosis of diseases

(1) Owners or managers of the livestock animals shall observe their animals daily and constantly be aware of their health conditions, and if any disorder should be noticed, shall promptly ask the veterinarians consultation.

(2) The veterinarian shall, with consideration for the characteristics and conditions of the patient animal, listen well to the owner or manager of the animal for the time of onset and course of disorder and measures taken by them. The veterinarian shall then make necessary clinical pathology test with blood, milk, or feces, and grasp the situation of disorder accurately, such as its causative agent (bacteria or virus) and the status of infection (primary or secondary infection), before deciding the treatment plan.

(3) Upon diagnosis, the veterinarian should take into consideration records of infections that occurred within the farm and neighboring regions, details and outcome of treatment that was conducted for such infection, and prognosis of the diseased animal. To help for any future diagnosis and selecting antibiotics, the diagnosis and the course of treatment should be recorded and kept in a medical treatment file.

(4) Efforts shall be made to search for the causative pathogen, by taking sample materials or the lesion from which causative agent is expected to be isolated and isolating bacteria. The isolated causative pathogen shall

also be put on antibiotic susceptibility test (※1, 2)

Upon selecting an antimicrobial, veterinarians can refer to the information on monitoring of antimicrobial resistant bacteria monitoring information (JVARM: Japanese Veterinary Antimicrobial Resistance Monitoring System in the Field of Animal Hygiene) listed in the MAFF National Veterinary Assay Laboratory website.

3. Selection and use of antimicrobials

For diagnosed infections described in the above 2, in cases where the veterinarian determines that it is necessary to use antimicrobials for such treatment, he/she should select an antimicrobial, taking into account the following matters and administer the antimicrobial appropriately: features of the target disease, results of antibiotic susceptibility testing, the antibiotic's efficacy to the concerned causative pathogen, regimen, pharmacokinetics, and appropriate withdrawal period.

Also, the veterinarian should take into consideration previous use and outbreaks of infections in the surrounding regions, as well as keep in mind particularly the matters set forth below, upon selection and use of antimicrobials:

(1) Antimicrobials should be used only for the minimum period necessary for treating the diseased animal, based on approved dosage, administration and indications and taking account of administration interval, administering period, and withdrawal period.

(2) To contain selection of antimicrobial resistant bacteria, a first-line antimicrobials should be selected from antimicrobials with the narrowest antibiotic spectrum among those that have shown effectiveness to causative bacteria by antibiotic susceptibility test. (※3)In general, broad-

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（※１） If the veterinarian determines that it is urgent, selecting and using an antimicrobial, after taking full account of the infection state within and around the farm of concern, may be unavoidable, but even in such cases, bacterial isolation and antibiotic sensitivity testing shall also be carried out at as a general rule.

（※２） Antibiotic susceptibility test: Antibiotic susceptibility test is important for acquiring stable antimicrobial treatment effect. Methods for antibiotic susceptibility test include ① Disk method ②Broth dilution method and ③ Agar plate dilution method. The results of antibiotic susceptibility tests shall be recorded and kept on file, and utilized when selecting appropriate antimicrobials.

（※３） In cases of emergency requested situations such as in ※1, if the pathogenic bacteria cannot be

spectrum antimicrobials show antibacterial activity in many species of microorganisms, resulting in an increased opportunity of selected antimicrobial resistant bacteria.

(3) Second-line antimicrobials (※4) such as fluoroquinolones and 3rd generation cephalosporins which are important antimicrobials for human healthcare should only be chosen when the first-line antimicrobial is ineffective.

(4) When deciding the route of administration, select the route that has lesser opportunity of exposure of antimicrobials to intestinal bacteria as far as possible.

(5) Use of unapproved medicines and off-label use for food producing animals shall not be allowed as a general rule. Also, pursuant to the Food Sanitation Act (Act No. 233 of 1947), substances not permitted to be in food, or other ingredients (※5)that may have adverse impact on human health shall be prohibited to be used in food producing animals.

(6) Administering antimicrobials to healthy livestock animals that may be in danger of infection, on the grounds that such infection exists in the region or such infection is found in part of the population, should be avoided as much as possible. Such administration shall only be carried out strictly on the responsibility of a veterinarian, under extremely restricted conditions, and only applies in cases such as the following: considering the probability of spread of infection, judged by the features of infection, history of infections within the farm of concern, immune state and herd/flock structure of the livestock, and whether or not vaccination or other means of epidemic prevention measures have been taken, it may most likely spread widely if such administration is not carried out.

(7) Concomitant use of antimicrobials should be avoided as far as possible (※

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separated, antimicrobials of the narrowest antibiotic spectrum shall be selected among the antimicrobials that are expected to be effective, judged from the sensitivity of the estimated pathogenic bacteria.

(※4) A list of antimicrobial agents approved as second-line medicines is shown in the MAFF National Veterinary Assay Laboratory website below:

URL : http://www.maff.go.jp/nval/risk/index.html (search for "second-line medicine" in the National Veterinary Assay Laboratory website)

(※5) Ingredients listed in the Ordinance on Veterinary Medicine and the Regulations on Use of Medical Supplies (Ministerial Ordinance of MAFF No. 44 as of 2013) attached list No. 3 and No. 4; and, the Ordinance on Provisions when not applying the Regulations on Prohibition of Use of Medical Supplies based on Pharmaceutical Affairs Act (Ministerial Ordinance of MAFF No. 70 as of 2003) attached list

[6], from the point that such use may encourage emergence of side effects due to strengthened toxicity; raise pharmacological competence that inhibits efficacy; and affect prohibition and withdrawal period.

Antibiotic feed additives may also affect the prohibition period and withdrawal period. Veterinarians shall grasp the amount and time for such feed; when administrating antimicrobials of the same ingredients, the veterinarian shall decide the amount, taking into account the ingredients in the feed.

(8) To strengthen an animal's immunity to pathogenic bacteria and to fully bring out efficacy of antimicrobials, in cases where the patient animal is exhausted and weak, or is in dehydrated condition due to diarrhea, symptomatic treatment (e.g. reinfusion) may be given along with the antimicrobials.

(9) Decision of whether to continue or change the antimicrobials shall be made by observing the treatment effect of the antimicrobial administered in the initial medical examination, watching carefully for changes in clinical signs after such administration. In cases of changing an antimicrobial, selection of antimicrobials shall be made based on the result of antimicrobial susceptibility test.

4. Sharing information among authorities and stakeholders

For a thorough implementation of responsible and prudent use of antimicrobials, it is important that all stateholders share the information on antimicrobial use. The veterinarians in particular should make efforts to grasp nationwide information, issued by the MAFF, on distribution amount and antimicrobial susceptibility circumstances. In addition, the veterinarians should make efforts to share information as set forth below, with not only veterinarians, but also regional livestock hygiene service centers, manufacturers and wholesalers, retailers, and producers.

(1) Information on outbreaks and course of infections, use of antimicrobials,

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(※6) In circumstances where, a pathogen cannot be identified, the antimicrobial of the first treatment is not effective, death rate or disease rate have evidently risen, or the patient animal's condition has become worse, concomitant use of antimicrobials may be required to expect multiplier effect and widening of antibiotic spectrum. In such cases too, antimicrobials should be administered only of the necessary amount.

its efficacy and antimicrobial susceptibility in the regions of administration

(2) Information on prevention and treatment of infections

(3) Information on pharmacokinetics of antimicrobials

(4) Notifications on using antimicrobials (e.g. limitation in administering period, use as second-line antimicrobial).

Ⅴ. References

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9) Code of Practice to Minimize and Contain Antimicrobial Resistance CAC/RCP61-2005

http://www.codexalimentarius.net/input/download/standards/10213/CXP_061e.pdf
10) Survey of antimicrobial susceptibility of bacteria from livestock
http://www.maff.go.jp/nval/tyosa_kenkyu/taiseiki/
11) Standards of rearing hygiene management based on Act on domestic animal infectious disease control
http://www.maff.go.jp/j/syouan/douei/eisei/e_koutei/kaisei_kadenhou/index.html
12) Guidelines for Use of Antimicrobial Agents in Livestock Mutual Aid
http://www.maff.go.jp/j/keiei/hoken/saigai_hosyo/s_yoko/
13) Guidelines for Establishing Risk Management Measures for Veterinary Antimicrobial Agents
http://www.maff.go.jp/j/syouan/tikusui/yakuzi/pdf/120322.pdf
14) Assessment Guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food producing animals
http://www.fsc.go.jp/senmon/hisiryou/taiseikin_hyoukasisin.pdf