

Guideline for Establishing Risk Management Measures for Veterinary Antimicrobial Agents

1. Introduction

Veterinary antimicrobial agents are important materials for protecting animal health and securing stable supply of safe food. However, there is persistent risk of human and veterinary healthcare impact by the antimicrobial resistant bacteria, which are selected through use of such antimicrobials. To minimize such risks, risk management measures should be established based on risk assessments. In Japan, with regard to veterinary antimicrobial agents used in food animals, risk assessments on human health impacts caused by antimicrobial resistant bacteria through food have been carried out in order since 2003 pursuant to the “Evaluation guidelines for health impact through food, caused by antimicrobial resistant bacteria that are selected by use of antimicrobial agents in livestock animals,” (Food Safety Commission Decision as of September 30, 2004; hereinafter, “Food Safety Commission Assessment Guidelines”). The Ministry of Agriculture, Forestry, and Fisheries (MAFF) has been implementing risk management for veterinary antimicrobial agents, based on the Pharmaceutical Affairs Act, the Act on Securement of Quality, Effectiveness, and Safety of Pharmaceuticals and Medical Devices (hereinafter, the Pharmaceutical and Medical Devices Act) and other related laws. In addition to this, a further examination of risk management measures should be considered, supported by risk assessment results based on the Food Safety Commission Assessment Guidelines.

Under this circumstance, securing food safety and efficacy of veterinary antimicrobial agents for livestock and aquatic animals, general guideline for establishing risk management measures based on scientific evidences to mitigate risks related to antimicrobial resistant bacteria has been made. This guideline would be applied to process of risk management from establishment to enforcement of risk management measures and “Standard Procedures for Risk Management on Food Safety for the MAFF and the MHLW” (as of August, 2005, by the MAFF and MHLW; hereinafter, “Risk Management Procedures”) must be refereed at each process. Because standard protocol of risk management for antimicrobial resistant bacteria has not been established, this guideline shows currently feasible risk management measures and will be revised if necessary, flexibly working out this guideline.

2. Definition

Terms used in this guideline are referred from the Risk Management Procedures and Food Safety Commission Assessment Guidelines and are defined as follows:

- Livestock and aquatic animals

Cattle, pigs, chickens, and aquatic animals

- Hazard

Antimicrobial resistant bacteria that are selected due to use of veterinary antimicrobial agents in livestock and aquatic animals

- Risk

Probability and extent that efficacy of treatment of human or veterinary antimicrobial agent is reduced or lost when antimicrobial resistant bacteria is transmitted to and is infected with human or livestock and aquatic animals.

- Risk management measures

Policy to reduce emergence of antimicrobial resistant bacteria

3. Purpose and intended animals

This guideline is aimed to establish effective risk management measures to mitigate risk associated with emergence of antimicrobial resistant bacteria due to use of veterinary antimicrobial agents in livestock and aquatic animals. Top priority is to mitigate negative effect to human health due to antimicrobial resistant bacteria and importance of veterinary antimicrobial agents on veterinary medicine should also be considered as long as safe food production is not impaired. This guideline is not applied to antimicrobial agents for pet animals.

4. Basic procedures for establishing risk management measures

Risk management measures are basically established taking into account result of risk assessment estimated by the Food Safety Commission. However, in cases when there is no time for the Food Safety Commission to perform risk assessment, the MAFF can provide a provisional estimate of risks if necessary. The MAFF must refer to the Food Safety Commission Assessment Guidelines when estimating provisional risks.

5. Materials for the establishment of risk management measures

Data on risk assessment of concerned veterinary antimicrobial agents (e.g. materials submitted to the Food Safety Commission based on

evaluation guideline of the Food Safety Commission and result of risk assessment) as well as factors for judgement to decide risk management measures (Table 1) are used when establishing risk management measures. Materials are compiled by MAFF with the cooperation to manufactures and wholesalers of veterinary antimicrobial agents or other related groups.

6. Establishment of risk management measures

(1) Feasible risk management measures

Table 2 shows current feasible risk management measures.

(2) Method of establishing risk management measures

① Step 1

Risk management measures is basically decided in accordance with risk category based on risk assessment result of the Food Safety Commission (high/medium/low/negligible). Table 3 shows concept of risk management measures according to risk category.

Strict risk management measures are necessary if high score is estimated in release assessment although risk categories are same.

② Step 2

Importance of concerned veterinary antimicrobial agents, existence of alternatives and alternative measures, secondary risk and other factors for judgement to decide risk management measures (Table 1) should be discussed in accordance with each livestock and aquatic animal which is subject to be admitted concerned veterinary antimicrobial agents and route of administration regarding risk management measures decided in step 1, and finally risk management measures would be decided.

7. Enforcement of risk management measures

Risk management measures will be enforced after the most feasible and effective management measure is decided among risk management measures selected in Step 2 above by deliberation of Committee on Animal Drugs. The decided risk management measures are reviewed through risk communication and public comment before its enforcement, if necessary.

Table 1 Factors for decision making when selecting risk management measures

| Factors for decision making | Description |
|---|---|
| Importance of antimicrobial agents on veterinary medicine | Severity of disease treated by concerned antimicrobial agent (e.g. spread of disease and disease state) and significance of antimicrobial agent for clinical veterinarians (e.g. usability, efficacy and cost) |
| Existence of alternatives and alternative measures | Existence of other antimicrobial agents clinically equivalent to concerned antimicrobial agents Existence of alternative measures such as vaccine |
| Secondary risks | 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 |
| Effect of reducing risk | Expected level of reducing risk of selecting antimicrobial resistant bacteria if risk management measures are enforced |
| Feasibility | Feasibility of risk management measures in terms of technical, administrative and financial aspects |
| Others | Any factors which should be considered because of characteristics of concerned antimicrobial agents |

Table 2 Feasible risk management measures

| Risk management measures | Effect |
|---|--|
| Revocation of approval to manufacture and sell | Concerned antimicrobial agents is discontinued to be distributed and used. |
| Provisional prohibition of use | The concerned antimicrobial agent shall be prohibited from being distributed (may not be used) within Japan for a certain period (assumed to be for a few years) |
| Deletion of dosage forms | If the concerned antimicrobial agent is approved for two or more dosage forms, some of such forms shall not be used |
| Deletion of targeted livestock and aquatic animal species | If the concerned antimicrobial agent is approved for two or more animal species, some of the species shall be deleted from targeted animals. Such species may be examined separately for each dosage form |
| Deletion of indication / indicated bacteria | If the concerned antimicrobial agent is approved for a number of indications /indicated bacteria, some of them shall be deleted. Such indications /indicated bacteria may be examined separately for each dosage form |
| Restriction of use in the latter half of feeding period | Restricting use during the latter half of feeding period, when larger amount of antimicrobial agents is needed per individual animal, shall reduce the total administration amount. This shall also contain the increase of resistant bacteria before shipping, caused by selective pressure due to use in latter feeding period |
| Shortening of the administration period | Amount of the antimicrobial agents administrated per individual animal shall be reduced by shortening of the administration period |
| Thorough implementation of use as a second-line drug | This is indicated in the notices of New quinolone antimicrobials or 3rd to latest generation cephalosporin antimicrobials. This requirement shall restrict second-line drugs from being used only for cases where the first-line drug is ineffective |
| Strengthening of the | Increasing monitoring frequency and data points |

| | |
|------------|---|
| monitoring | shall contribute to prompt detection of development of resistance |
| Others | Risk management measures shall be considered as necessary, corresponding to the features of the antimicrobial agents. |

Table 3 Perspectives for risk management measures for each risk estimate division

| Risk management policy | Category | Examples of risk management measures |
|------------------------------------|------------|--|
| Strengthen risk management measure | High | Revocation of approval Provisional prohibition of use Deletion of dosage forms Deletion of targeted livestock and aquatic animals |
| | Medium | Deletion of indication/ indicated bacteria 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 |
| Continue risk management measure | Low | Continue monitoring |
| | Negligible | |

References

Food Safety Commission's Perspectives on determining risk estimates

| Outcomes of the risk assessment components | | | Divisions of estimated risks |
|--|----------------------|-------------------------|------------------------------|
| ○Release assessment | ○Exposure assessment | ○Consequence assessment | |
| Scores | Scores | Scores | |
| High (3) | High (3) | High (3) | |
| Medium (2) | Medium (2) | Medium (2) | |
| Low (1) | Low (1) | Low (1) | |
| Negligible (0) | Negligible (0) | Negligible (0) | |
| •Total scores 8~9 | | | High |
| •Total scores 5~7 | | | Medium |
| •Total scores 2~4 | | | Low |
| •Total scores 0~1 | | | Negligible |

Release assessment: To assess the potential of hazard to be selected and the degree, in the case where a veterinary antimicrobial was use in livestock animals

Exposure assessment: To explain the route of hazard exposure in humans, and assess the potential of the hazard arising and the degree of the same

Consequence assessment: To explain the relationship between the exposure of the identified hazard to humans and the consequences of such exposure in the same, and to assess the potential of human antimicrobials to have reduced or no treatment benefit and the degree