Provisional translation

Approved by the Food Safety Commission on September 30, 2004

Assessment guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food-producing Animals

Chapter 1 General Rules

1. Introduction

Antimicrobials have been used in the process of food producing animal or fish farming in Japan for more than half a century. The purposes are either to “improve feed efficiency and promote growth, etc. in food producing animal” as “feed additives” based on the “Law Concerning Safety Assurance and Quality Improvement of Feeds (Law No. 35, 1953) or to “treat diseases” as “veterinary medicinal products” based on the “Pharmaceutical Affairs Law” (Law No. 145, 1960).

It is well known that antimicrobial-resistant bacteria are selected by the use of antimicrobials[1]. Therefore these days, both in Japan and abroad, there are questions regarding the potential of these antimicrobial-resistant bacteria, especially in farming, to be selected for resistance and to spread that resistance among humans through food commodities; thus, affecting human health. The Office International des Epizooties (OIE), Food and Agriculture Organization of the United Nations / World Health Organization (FAO / WHO), and various international organizations in the European Union (EU) and the U.S., etc. have been performing investigations to develop risk analyses and preparing guidelines regarding antimicrobial-resistant bacteria derived from food producing animals, and, in some cases, actually working on risk analyses. Moreover, from the aspect of health protection in both animals and humans, the “responsible and prudent use” of veterinary antimicrobials, in order to suppress and reduce the selection of antimicrobial resistance, as well as the collection of further information regarding antimicrobial-resistant bacteria, have been encouraged, mainly by international organizations, food producing animal producers and the animal health industry.

Based on this background, in December 2003, the Food Safety Commission was required by the Ministry of Agriculture, Forestry and Fisheries of Japan to scientifically assess the potential and degree of antimicrobial-resistant bacteria, which were selected by antimicrobials used as feed additives or veterinary medicinal products, for potential harm to human health through food commodities. Thus, an assessment guideline, describing the criteria considered necessary to assess

[1] Survival and proliferation of antimicrobial-resistant bacteria coexisting in a group of antimicrobial-susceptible bacteria due to the use of certain antimicrobials.

the effect of antimicrobial-resistant bacteria on human health through food commodities, was established referring to the “OIE International Standards on Antimicrobial Resistance, 2003 (OIE International Standards)”.

The issues of antimicrobial-resistant bacteria are assumed to be significant factors for concerns regarding food commodities or the environment; for instance, waterborne infections, etc. The Food Safety Commission recognizes these as difficult issues, which involve various factors in complex ways. Furthermore, at this time, it is uncertain whether detailed information and findings have been adequately accumulated for antimicrobial-resistant bacteria, even in the field associated with food production by itself. Thus, the Food Safety Commission decided to conduct assessments based on available scientific findings, etc., along with this guideline, in order to assess the effect of food-borne resistant bacteria on human health, as requested by the Ministry of Agriculture, Forestry and Fisheries of Japan.

This guideline is based on factors similar to those in the risk assessment method suggested by the CAC (Codex Alimentarius Commission), which has been generally used as an evaluation method for safety regarding food commodities. The guideline was based on the corresponding descriptions of the OIE International Standards, which had been considered appropriate in assessing the effect of food producing animal-derived antimicrobial-resistant bacteria on health through food commodities. At the same time, other guidelines suggested in Japan or abroad (listed in “references”) were consulted to achieve international consistency and establish the most appropriate guideline to use in Japan.

2. Definitions for this guideline

The terms used in the assessments are defined according to the OIE International Standards, etc.

(1) Antimicrobials

Antimicrobials are chemical substances which show antimicrobial activity against microbes such as bacteria, including antibiotics and synthetic antimicrobial agents.

In this guideline, the antimicrobials used in medical practice are called “human antimicrobials” while those used in food producing animal and aquaculture are called “veterinary antimicrobials”. Veterinary antimicrobials include the following two types:

- Antimicrobial feed additives designated or requested to be designated by the Minister of the Ministry of Agriculture, Forestry and Fisheries of Japan, under article 2, section 3 of the “Law Concerning Safety Assurance and Quality Improvement of Feeds (Law No. 35, 1953).
- Veterinary medicinal products, of which the main ingredients are antimicrobials, approved or for which approval is requested by the Minister of the Ministry of Agriculture, Forestry and Fisheries of Japan, based on article 14, section 1 of the “Pharmaceutical Affairs Law” (Law No. 145, 1960),

which was applied accordingly by the regulation described in article 83, section 1 of the same law (including the case applied in article 23), as well as article 19, section 1 of the same law.

(2) Food producing animals

For feed additives: cattle, swine, chickens and quails [animals listed in article 1 of the "Enforcement Ordinance for Secure Safety and Quality Improvement of Feeds (ordinance number 271, dated June 20, 2003)" and allowed to receive feeds containing antimicrobial feed additives].

For veterinary medicinal products: cattle, horses, swine, chickens, quail, and honeybees, as well as aquacultural species that are farmed for human consumption [animals and species listed in article 8-2-2 of the "Veterinary Medical Products Regulation Law (Ministry of Agriculture and Forestry, Law No. 3, 1961)"].

(3) Hazard

Hazard is defined as a risk factor against humans, indicating antimicrobial-resistant bacteria selection as a consequence of the use of antimicrobials in food producing animals.

For antimicrobial-resistant bacteria having acquired resistance due to antimicrobial resistance determinants[2], the corresponding factors must also be considered.

(4) Risk

The potential of human antimicrobials to have reduced or no treatment benefit and the degree of loss, in the case where a human has developed an infection caused by antimicrobial-resistant bacteria, which have been selected by the use of veterinary antimicrobials in food producing animal production and transmitted to the human through food commodities.

(5) Hazard identification

To identify a hazard being subjected to the risk assessment based on available information.

Corresponds to the Hazard Identification of the OIE International Standards.

(6) Risk assessment

To assess a risk by going through each of the following steps: release assessment, exposure assessment, consequence assessment and risk estimation. To assess the potential of human antimicrobials to have reduced or no treatment benefit and the degree of loss, in the case where a human has developed an infection caused by antimicrobial-resistant bacteria, which were transmitted to the human through food commodities.

Corresponds to the Risk Assessment of the OIE International Standards.

(7) Release assessment

To assess the potential of hazard to be selected and the degree, in the case where a veterinary antimicrobial was used in food producing animal production.

Corresponds to the Release Assessment of the OIE International Standards.

(8) Exposure assessment

[2] Antimicrobial-resistant plasmid, etc., which provides an antimicrobial resistance property to other bacteria.

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

Corresponds to the Exposure Assessment of the OIE International Standards.

(9) 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.

Corresponds to the Consequence Assessment of the OIE International Standards.

(10) Risk estimation

To estimate the risk induced by the identified hazard by cumulatively evaluating the results obtained from the release assessment, exposure assessment and consequence assessment.

Corresponds to the Risk Estimation of the OIE International Standards.

(11) Qualitative risk assessment

Assessment in which the result of risk assessment is described in qualitative terms, such as “high”, “medium”, “low” or “negligible”.

(12) Semi-quantitative risk assessment

Assessment in which the result of risk assessment is described semi-quantitatively by using a scoring method.

(13) Quantitative risk assessment

Assessment in which the result of risk assessment is described by numerical values, such as the incidence, duration of disease and the severity or ineffectual rate of treatment, etc.

3. Objectives and Subjects

This guideline is established to assess the potential and degree of antimicrobial-resistant bacteria, which may be selected in the case where veterinary antimicrobials are used in food producing animals, and the potential effect on human health of food commodities.

Since veterinary antimicrobials are used in the process of rearing food producing animals, the subjects include “animal and aquatic food commodities”[3]. The cases in which animal and aquatic food commodities are not involved, for instance, direct transmission (infections) caused by contact with food producing animals infected by these bacteria, or transmission (infections) caused by environmental circulation via air or contaminated tools, are not to be included.

Water is not included as a subject in this guideline, since it was considered extremely difficult at this point to scientifically assess the condition of contamination, given the lack of information or findings; though there may be potential for neighboring rivers around farms or well water to be contaminated by antimicrobial-resistant bacteria derived from food producing animals.

[3] Food commodities defined as items such as farm meat, eggs, milk and fish meat derived from food animals.

4. Basic Procedures to Assess the Effect of Food on Health

The assessment of the effect of food on health is performed by the identification of hazards and the subsequent risk assessment.

Risk assessment consists of the following: release assessment, exposure assessment, consequence assessment and risk estimation (Figure).

In risk estimation, a cumulative evaluation is performed on the items from each assessment step.

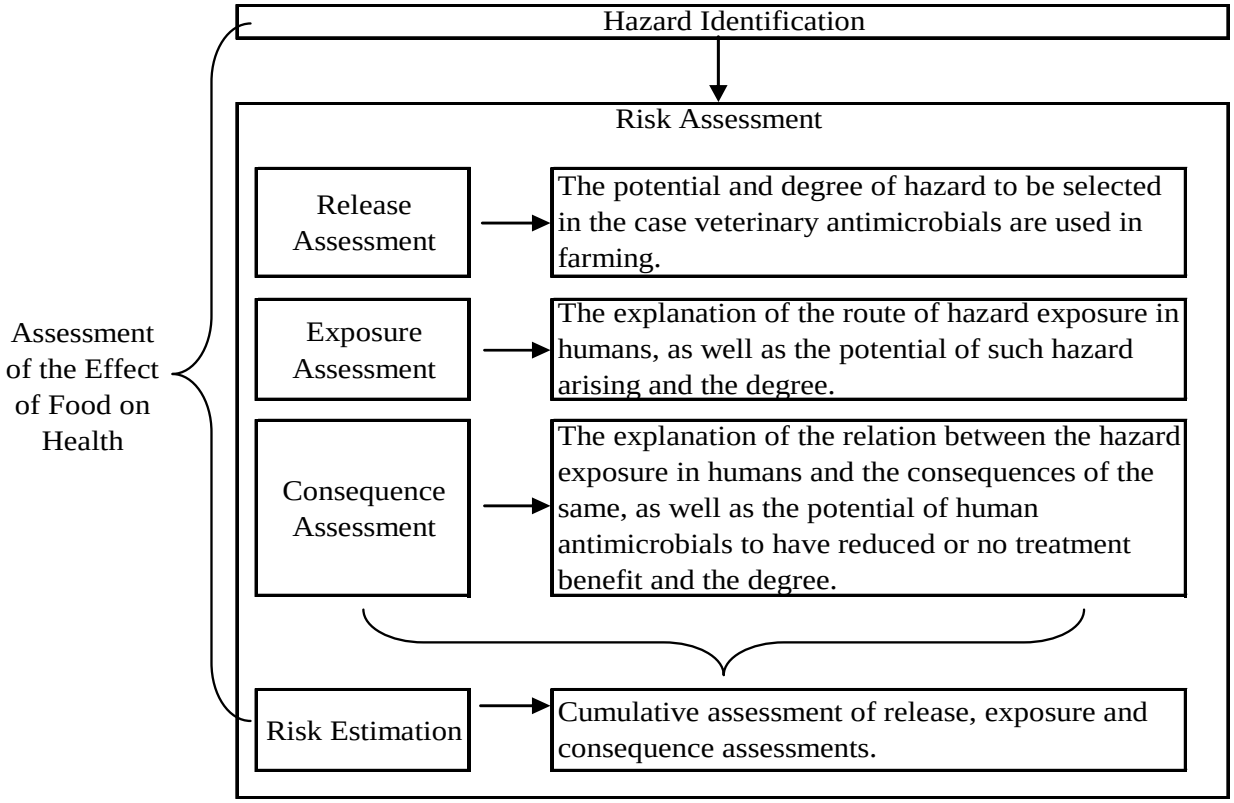

Figure Procedures to Assess the Effect of Food on Health

In principle, the Food Safety Commission is to perform a qualitative risk assessment. However, according to the results obtained in the qualitative assessment, semi-quantitative or quantitative risk assessments will be performed once the data are collected and investigated in detail and when it is considered that the subjected veterinary antimicrobials need to be assessed semi-quantitatively or quantitatively.

5. Materials used in the Assessment

The person[4] preparing the materials needs to collect information regarding the items described

[4] The Ministry of Agriculture, Forestry and Fisheries of Japan and the manufacturers of veterinary antimicrobials, etc.

in Chapter 2 as much as possible and submit them as supportive materials. In cases where the submission of materials, etc. is difficult or when other information is used in place of the materials, for inevitable reasons, scientific and rational reasoning must be presented.

Furthermore, results obtained in the study conducted by the person preparing the materials, or references, including strictly (peer) reviewed published works, etc. should be accepted as supportive materials. The results of the study conducted by the person preparing the materials, in principle, should be those obtained by highly reliable methods. In addition, the study must have been conducted at a laboratory or facility where adequate facilities, equipments and faculty members necessary to be recognized as a reliable facility are available, as in a GLP compliant test facility, and where the operation has been confirmed to be appropriately controlled. When materials which do not meet the conditions described above are to be used, the reasons and rationale for such use must be clearly stated.

The Food Safety Commission might require the person preparing the materials to provide additional information, or collect materials by themselves as the need arises.

6. Revision of Guideline

The Food Safety Commission considers that it will be necessary to have further discussions regarding information or findings associated with antimicrobial-resistant bacteria selected by veterinary antimicrobials used in food producing animal production, as well as the related antimicrobial resistance determinants. This guideline is to be reviewed, if necessary, when new scientific facts are revealed through improvement of various study methods, improved investigational technologies to obtain new data related to these issues, or by data collection through monitoring, etc.

Chapter 2 Detailed Expositions

Part 1. Hazard identification

In hazard identification, antimicrobial-resistant bacteria, which might develop as a consequence of using veterinary antimicrobials in food producing animals, and which could be the risk factor against human health via food commodities, are to be identified. For antimicrobial-resistant bacteria having acquired antimicrobial resistance property due to antimicrobial resistance determinants, those factors must also be considered.

Since this step is significant when performing the risk assessment, the examination procedures need to be described in detail for both bacteria identified as possible hazards or for those bacteria not identified as such.

When identifying hazards, pathogenic bacteria in food producing animals subjected to the use of veterinary antimicrobials, pathogenic bacteria subjected for medical treatments, indicator

bacteria[5] (*Enterococcus*, *Escherichia coli*, etc.) as well as food-commodity-derived pathogenic bacteria (*Salmonella*, *Campylobacter,* pathogenic *E. coli*, *Vibrio parahaemolytius*, *Listeria*, etc.) are to be included in the investigation.

Hazard is, for instance, identified based on the following materials regarding veterinary antimicrobials, and the discussions made on the hazard identification are summarized in the table presented in the attachment.

1. Information regarding veterinary antimicrobials

(1) Name: generic name, chemical name, CAS number, etc.

(2) Chemical structure: structural formula, molecular formula, molecular weight, etc.

(3) Type of active ingredients: type of active ingredients, the related types

(4) Administration method

a. Veterinary medicinal products: subjected food producing animals, administration route, dosage and administration, precaution and withdrawal period, etc.

b. Feed additives: kind of feed permitted to be added, concentration in the feed; the names of feed additives and the amount being added as well as precautions, etc. when more than two kinds of feed additives have been added to the same feed.

(5) *In vivo* pharmacokinetics of veterinary antimicrobials in subjected food producing animals.

(6) Antimicrobial activity: action mechanism of antimicrobial activity, type of action (bactericidal or bacteriostatic), antimicrobial spectrum, pathogenic bacteria in food producing animals subjected to the use of veterinary antimicrobials.

(7) Distribution of the minimum inhibitory concentration or the minimum bactericidal concentration against pathogenic bacteria in food producing animals subjected to the use of veterinary antimicrobials, as well as indicator bacteria and food-commodity-derived pathogenic bacteria (data for standard strain[6] , or for type strain[7] and wild type strain).

2. Overview of related human antimicrobials

(1) Names and chemical structural formulas of antimicrobials, which have similar chemical structures and those which might cause cross-resistance.

(2) Efficacy and importance of human antimicrobials described in (1), in the clinical settings.

a. Degree of importance as a treatment option against serious infections, highly significant

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[5] Bacteria which are widely used as antimicrobial susceptibility indicators in assessments of veterinary antimicrobials. Bacterial species, not associated with animal derived infections, but living in animal intestinal tracts and transmitted to humans through the food chain. These bacteria do not usually induce food-derived infections in humans.

6 Microbial strains which become standards to identify microbial species.

7 Microbial strains used in various research, including assessments of antimicrobials, etc. and retained at publishing organizations, such as the ATCC (The American Type Culture Collection) or the National Institute of Infectious Diseases, etc.

infections in terms of public health, and food commodity derived infections.

b. Incidence of infection specified in a.

c. Presence or absence of alternative substance/s and name/s.

3. Information regarding antimicrobial-resistant bacteria as well as antimicrobial resistance determinants

(1) Information regarding the resistance mechanism and antimicrobial resistance determinants

(2) Cross-resistance with related human antimicrobials, etc. described in 2.

Part 2. Risk Assessment

Risk assessment is performed by estimating the risk associated with the identified hazard by considering the results of the release, exposure and consequence assessments, cumulatively. The discussion engaged in during the assessment at each step and the risk estimation are to be summarized in a list presented in the attachment.

1. Release assessment

The target of release assessment is to be from the point at which a veterinary antimicrobial has been used in food producing animals until the food producing animal or the animal and aquatic food commodities produced by the corresponding food producing animals are shipped from the farm or fish farm.

The potential and degree of hazard to be selected when a veterinary antimicrobial is used in food producing animals are assessed.

Release assessment is conducted based on, for instance, the information listed below:

(1) Information regarding veterinary antimicrobials

1. Name: generic name, chemical name, CAS number, etc.

2. Chemical structure: structural formula, molecular formula, molecular weight, etc.

3. Type of active ingredients: type of active ingredients, related types

4. Name and characteristics of the product of which the main ingredient is a veterinary antimicrobial: purity, form, types and ratio of excipients, dissolvability and deliverability. For feed additives, the distinction between the feed grade or refined grades, etc.

5. Administration method

a. Veterinary medicinal products: subjected food producing animals, administration route, dosage and administration, precaution and withdrawal period, etc.

b. Feed additives: kind of feed permitted to be added, concentration in the feed, the names of feed additives and the amount being added as well as precautions, etc. when more than two kinds of feed additive have been added to the same feed.

6. *In vivo* pharmacokinetics of veterinary antimicrobials in subjected food producing

animals.

7. Antimicrobial activity of veterinary antimicrobials: action mechanism of antimicrobial activity, type of action (bactericidal or bacteriostatic), antimicrobial spectrum, pathogenic bacteria in food producing animals subjected to the use of veterinary antimicrobials.

8. Susceptibility distribution of the corresponding bacteria, including hazard

a. Distribution of the minimum inhibitory concentration or the minimum bactericidal concentration against the corresponding pathogenic bacteria, including hazard (data for standard strain[6] or for type strain[7] and wild type strain).

b. Conditions of development of antimicrobial-resistant bacteria in food producing animal farming or fish farming settings.

(2) Information regarding the development of hazard

1. Resistance mechanism of hazard (inactivation of antimicrobials, change in the target molecular of antimicrobials, decrease in the intake of antimicrobials, excretion of antimicrobials, etc.)

2. Genetic information of hazard

3. The antimicrobial resistance acquirement rate (mutation rate) in the spontaneous mutation and the speed [indicating information regarding multiple strains to be investigated (origins, etc.) and the rate at which those strains are acquired].

4. The potential for inter-bacterial transmissions of antimicrobial resistance determinants.

5. Resistance selection pressure[8]: overview of human antimicrobials with which the hazard might show cross-resistance (name, chemical structural formula, administration method and dosage, etc.)

(3) Information regarding the amount being used

1. Amount of distribution of veterinary antimicrobials (actual amount; overall or by food producing animals)

2. The amount being manufactured (imported) or sales (overall or by food producing animals)

3. Timing to start the marketing

2. Exposure assessment

The target of exposure assessment is to be from the point at which the food producing animal or animal and aquatic food commodities are shipped from the farm or fish farm, delivered, slaughtered and processed, etc. to the point at which a human receives these food producing animals or food commodities and consumes them.

The routes of hazard exposure in humans are to be clarified, and the increase or decrease of the

[8] Propensity to select antimicrobial-resistant bacteria.

hazard is to be estimated for each route. The potential and the degree of hazard exposure through animal and aquatic food commodities are also to be estimated.

The assessment of hazard is, for instance, conducted based on information, etc. described below.

(1) Information regarding biological features of the hazard

1. Resistance[9], survivability[10], and reproducibility of the hazard

2. *In vitro* (artificial culture medium, etc.) survivability and distribution of the hazard

3. The potential of the hazard settling down as human intestinal flora

4. The potential of antimicrobial resistance determinants being transmitted to the human resident bacteria or pathogenic bacteria.

(2) Information regarding the route from the point at which food producing animals or the animal and aquatic food commodities are shipped from the farm or fish farm to the point at which they are consumed

1. The route from the point at which food producing animals or the animal and aquatic food commodities are shipped from the farm or fish farm to the point at which they are consumed

2. The process at each step (slaughtering, processing, preserving, shipping, marketing and cooking, etc.) in the route

3. Change in the survivability and distribution of the hazard due to 2.

(3) Information regarding the animal and aquatic food commodities

1. The amount of annual consumption of animal and aquatic food commodities per person

2. The potential for the animal and aquatic food commodities to be contaminated by hazard before preparation, etc. or the condition of contamination.

3. Consequence assessment

The relation between the hazard exposure in humans and the resulting phenomena is clarified in the consequence assessment. Considering the possible consequences of hazard exposure on human health as well as the importance of human antimicrobials in medical treatments, the potential to have reduced or no treatment effect and the degree of loss are estimated.

The consequence assessment is conducted based on, for instance, the information, etc. described below.

(1) Human disease which might develop due to hazard exposure

1. Human disease which might develop due to exposure to hazard

2. Condition when the corresponding disease is developed, and the cause

[9] Degree of survivability of bacteria against heat or acid, etc.

[10] The degree of survivability of bacteria for extended periods under frozen or dry conditions, etc.

3. The seriousness of the corresponding disease

4. Conditions for pathogenic bacteria of the corresponding disease acquiring antimicrobial resistance

5. Conditions of measures to be taken against infection associated with 4.

(2) Treatment of the corresponding disease using human antimicrobials

1. The first choice treatment for the corresponding disease and the significance

2. The consequence of hazard[11] against the first choice treatment

3. The presence or absence of alternative treatment, and its future perspective as the first choice drug

4. Risk estimation

In risk estimation, the risk induced by an identified hazard is cumulatively estimated, based on the results obtained in the release, exposure and consequence assessments. The potential for human antimicrobials to have reduced or no treatment benefit and the degree of loss, in the case where a human has developed an infection caused by antimicrobial-resistant bacteria, which were selected as a consequence of using veterinary antimicrobials in food producing animals and transmitted to the human through food commodities.

Part 3. Other discussions

The Food Safety Commission is to discuss measures to be taken for the risk control, if necessary, based on the results obtained in the assessment of the effect of food on health.

[11] Influence on treatment effects.

(Attachment)

A summary table regarding hazard identification and each assessment, as well as the risk estimation

Table 1 Hazard Identification

Items	Overview of investigations
Name and chemical structure of veterinary antimicrobials	Summarize based on information obtained in Part 1, 1 (1) – (3).
Administration method	Summarize based on information obtained in Part 1, 1 (4).
In vivo pharmacokinetics of veterinary antimicrobials in subjected food producing animals	Summarize based on information obtained in Part 1, 1 (5).
Action mechanism and the type of antimicrobial activity	Summarize based on information obtained in Part 1, 1 (6)
Antimicrobial spectrum and the distribution of antimicrobial-susceptible bacteria	Summarize based on information obtained in Part 1, 1 (6) and (7)
Human antimicrobials which might cause cross-resistance in humans and the importance	Summarize based on information obtained in Part 1, 2 (1) and (2)
Information regarding antimicrobial-resistant bacteria and antimicrobial resistance determinants	Summarize based on information obtained in Part 1, 3 (1) and (2) (Resistance mechanism and the location of antimicrobial resistance determinants which express these mechanisms are clarified for the human antimicrobials described in Part 1, 2 (1)).

Table 2 Release Assessment

Items	Overview of Investigations
In vivo pharmacokinetics of veterinary antimicrobials in subjected food producing animals	Summarize based on information obtained in Part 2, 1 (1) 6

Action mechanism and the type of the antimicrobial activity	Summarize based on information obtained in Part 2, 1 (1) 7
Antimicrobial spectrum and the distribution of antimicrobial-susceptible bacteria	Summarize based on information obtained in Part 2, 1 (1) 7 and 8
Information regarding the resistance mechanism of antimicrobial-resistant bacteria and antimicrobial resistance determinants	Summarize based on information obtained in Part 2, 1 (2) 1 - 4 (Resistance mechanism specified in Part 2, 1 (2) a – d and the location of antimicrobial resistance determinants which express these mechanisms are clarified).
Resistance selection pressure	Summarize based on information obtained in Part 2, 1 (2) 5 (Organize according to the resistance mechanism specified in Part 2, 1 (2) a)
The amount of veterinary antimicrobials to be used	Summarize based on information obtained in Part 2, 1 (3)

Table 3 Exposure Assessment

Items	Overviews of investigations
Biological features of hazard	Summarize based on information obtained in Part 2, 2 (1)
The route for the animal and aquatic food commodities to be shipped from the farm, etc. and consumed, and the distribution of hazard by the process	Summarize based on information obtained in Part 2, 2 (2)
The amount of the animal and aquatic food commodities consumption and the condition of contamination	Summarize based on information obtained in Part 2, 2 (3)

Table 4 Consequence Assessment

Items	Overview of investigations
Human disease which might be	Summarize based on information obtained in Part 2,

induced by the exposure	3 (1)
Treatment of the corresponding disease using human antimicrobials	Summarize based on information obtained in Part 2, 3 (2)

Table 5 Risk Estimation

Hazard identification and Assessment Step	Discussions and Conclusions
Hazard identification	
Release assessment	
Exposure assessment	
Consequence assessment	
Risk estimation	

References

1）OIE International Standards on Antimicrobial Resistance, 2003.

2）Principles and guidelines for the conduct of microbiological risk assessment, Codex Alimentarius Commission (Codex)(1999).

3) Guideline for Risk Assessment on the effect of Public Health caused by Antimicrobial Resistance selected by the Use of Antimicrobials as Feed Additives in Livestock, Ministry of Agriculture, Forestry and Fisheries Agricultural Materials Council (June, 2003)

4) Guidance on Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance (VICH).

5) Guidance for industry # 152 - U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine, October 30, 2003.

6）Guideline on pre-authorization studies to assess the potential for resistance resulting from use of antimicrobial veterinary medicinal products EMEA/CVMP/244/01, European Agency for the Evaluation of Medicinal Products.

7） Part 10 of Veterinary Requirement Series, Submission to working party on antibiotics, National Registration Authority for Agricultural and Veterinary Chemicals, Australia, June 2000.

8) Report of the Consultation with Stakeholders on the Development of a Risk Management Strategy on Antimicrobial Resistance Associated with Animal Use of Antimicrobial Agents, Gantineau, QUEBEC, May 22-23, 2003, Veterinary Drugs Directorate, Health Canada.

9) The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans, Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR), Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry-AUSTRALIA.

10) The Reconsideration of the Registration of Products Containing Virginiamycin and Their Labels (Draft Review Report), March 2003, Australian Pesticides & Veterinary Medicines Authority.

11) Emergence of a Debate : AGP's and Public Health, Human Health and Antibiotic Growth Promoters(AGP) : Reassessing the Risk, HAN（FEFANA）

12） Qualitative Risk Assessment for Antibiotic Resistance, **“**Case study: *Salmonella* Typhimurium and the Quinolone/Fluoroquinolone class of antimicrobials”, Report and Qualitative Risk Assessment by the Committee for Veterinary Medicinal Products, EMEA/CVMP, (1999).