CHAPTER 6.10.

USA COMMENTS

(Note: recommended changes indicated in blue font)

RISK ANALYSIS ~~ASSESSMENT~~ FOR ANTIMICROBIAL RESISTANCE ARISING FROM THE USE OF ANTIMICROBIAL AGENTS IN ANIMALS

Article 6.10.1.

Recommendations for analysing the risks to animal and human ~~public~~ health from antimicrobial resistant micro-organisms of animal origin

1. Introduction

Problems related to antimicrobial resistance are inherently linked to antimicrobial use in any environment, including human and non-human usages. However, the emergence of antimicrobial resistance can occur through factors other than use of antimicrobial agents.

The use of antimicrobial agents for ~~therapy~~ therapeutic and non therapeutic purposes ~~, prophylaxis and growth promotion~~ in *animals* can reduce their efficacy in animal and human medicine, through the development of antimicrobial resistant strains of pathogenic micro-organisms. This *risk* may be represented by the loss of therapeutic efficacy of one or several antimicrobial agents ~~drugs~~ ~~*"and includes the selection and dissemination of antimicrobial resistant micro-organisms"*~~ ~~*emergence*~~ ~~of multi-resistant micro-organisms~~.

Recommended changes: The United States recommends changing the phrase "and includes the selection and dissemination of antimicrobial resistant micro-organisms." This phrase is probably incorrect in the context that is used and is not consistent with the principle of risk analysis.

- **Option one: delete the phrase; or**
- **Option two: replace the phrase with "…due to antimicrobial resistant micro-organisms".**

Rationale: Article 6.10.1, Section 1 (Introduction), the 2nd sentence in 2nd paragraph.

- In risk analysis, risk is understood to be the probability of a pre-defined harm caused by a given hazard. In this paragraph, hazard is mixed with risk. These two elements should be separate.
- In this document, resistant micro-organisms (whether they are newly emerged or are selected and disseminated) are **'hazard'** in this context, which is defined in the document (on page 1, item 4. Hazard identification). Thus, if the document also says the 'risk' includes the selection and dissemination of antimicrobial resistant micro-organisms as it currently states, it would contradict the definition of 'Hazard' with respect to antimicrobial resistance in this document as well as under the … (continued in text box below)

Rationale continued:

The OIE Terrestrial Code, Chapter 2.1, Import Risk Analysis.

- Whether or not the hazard (i.e., resistant micro-organisms) cause any harm will be determined through a risk assessment process. The likelihood of causing harm to humans by the hazard is assessed, for example, through certain exposure pathway (such as foodborne pathway) and its exposure assessment.
- In summary, 'hazard' is not equal to 'risk'. We believe this distinction is important and may help clarify between perceived risk (as demonstrated by presence of resistant micro-organisms) and actual risk as determined through science-based approaches and procedures.

2. Objective

The principal aim of *risk analysis*, for the purpose of this chapter, ~~for antimicrobial resistance in micro-organisms from *animals*~~ is to provide OIE Member Countries~~s~~ with a transparent, objective and scientifically defensible method of assessing and managing the human and animal health *risks* associated with the development of resistance arising from the use of antimicrobial agents in *animals*.

3. The risk analysis process

The principles of *risk analysis* are described in Chapter 2.1. ~~Section~~ of this *Terrestrial Code*. The components of risk analysis described in this chapter are *hazard identification*, *risk assessmsent*, *risk management* and *risk communication.*

~~A qualitative risk assessment should always be undertaken. Its outcome will determine whether progression to a quantitative risk assessment is feasible and/or necessary.~~

4. Hazard identification

Hazard identification is defined under the OIE *Terrestrial Code* Chapter 2.1.

For the purpose of this chapter, the *hazard* is the resistant micro-organism or resistance determinant that emerges as a result of the use of a specific antimicrobial agent in *animals*. This definition reflects the development of resistance in ~~a species of pathogenic~~ micro-organisms, as well as the development of a resistance determinant that may be passed from one species of micro-organism~~s~~ to another. The conditions under which the *hazard* might produce adverse consequences include any scenarios through which humans or *animals* could become exposed to a pathogen which contains that resistance determinant, fall ill and then be treated with an antimicrobial agent that is no longer effective because of the resistance.

5. Risk assessment

The *assessment of the risk* to human and animal health from antimicrobial-resistant micro-organisms resulting from the use of antimicrobials in *animals* should examine:

a) the likelihood of emergence of resistant micro-organisms arising from the use of antimicrobial(s), or more particularly, dissemination ~~production~~ of the resistance determinants if transmission is possible between micro-organisms;

b) consideration of all pathways and their importance, by which humans could be exposed to these resistant micro-organisms or resistance determinants, together with the ~~possible degree~~ likelihood of exposure;

c) the consequences of exposure in terms of *risks* to human and~~/or~~ animal health.

The general principle of risk assessment as defined in Chapter 2.1. of the *Terrestrial Code* applies equally to both qualitative and quantitative risk assessment. At a minimum, a qualitative risk assessment should always be undertaken.

Article 6.10.2.

Analysis of risks to human health

1. Definition of the risk

The *infection* of humans with micro-organisms that have acquired resistance to a specific antimicrobial agent due to the use~~d~~ in *animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the human *infection*.

2. Hazard identification

- Micro-organisms that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial agent(s) in *animals*.

- Micro-organisms having obtained a resistance determinant(s) from other micro-organisms which have acquired resistance arising from the use of an antimicrobial agent(s) in *animals*.

The identification of the *hazard* must include consideration of the class or subclass of the antimicrobial agent(s). This definition should be read in conjunction with point 4) of Article 6.10.1.

3. Release assessment

A release assessment describes the biological pathways necessary for the use of a specific antimicrobial agent in *animals* to lead to the release of resistant micro-organisms or resistance determinants into a particular environment, and estimating either qualitatively or quantitatively the probability of that complete process occurring. The release assessment describes the probability of the release of each of the potential *hazards* under each specified set of conditions with respect to amounts and timing, and how these might change as a result of various actions, events or measures.

The following factors should be considered in the release assessment:

- species of animal treated with the antimicrobial agent(s) in question;
- number of *animals* treated, sex, age and their geographical distribution ~~of those *animals*~~;
- prevalence of *infection* or *disease* for which the antimicrobial agent is indicated in the target animal population;
- data on trends in antimicrobial agent use and changes in farm production systems;
- potential extra-label or off-label use;
- ~~variation in~~ methods and routes of administration of the antimicrobial agent(s);
- dosage regimen including duration of use;
- ~~the~~ pharmacokinetics or pharmacodynamics ~~/pharmacokinetics~~ of the antimicrobial agent(s);
- ~~micro-organisms developing resistance as a result of the antimicrobial(s) use~~ pathogens that are likely to acquire resistance in animal host;
- commensal bacteria which are able to transfer resistance to human pathogens;
- mechanisms and pathways of direct or indirect transfer of resistance;
- potential linkage of virulence attributes and resistance;
- cross-resistance ~~and/~~or co-resistance with other antimicrobial agents;
- data on occurrence of resistant micro-organisms through surveillance of *animals*, products of animal origin and animal waste products ~~for the existence of resistant micro-organisms~~.

4. Exposure assessment

An exposure assessment describes the biological pathways necessary for exposure of humans to the resistant micro-organisms or resistance determinants released from a given antimicrobial use in *animals*, and estimating the probability of the exposures occurring. The probability of exposure to the identified *hazards* is estimated for specified exposure conditions with respect to amounts, timing, frequency, duration of exposure, routes of exposure and the number, species and other characteristics of the human populations exposed.

The following factors should be considered in the exposure assessment:

- human demographics and food consumption patterns, including traditions and cultural practices in respect to the preparation and storage of food;
- prevalence of resistant micro-organisms in food at the point of consumption;
- microbial load in contaminated food at the point of consumption for quantitative risk assessment;
- environmental contamination with resistant micro-organisms;
- prevalence of animal feed contaminated with resistant micro-organisms;
- transfer ~~cycling~~ of resistant micro-organisms between humans, *animals* and the environment;

- ~~steps~~ measures taken for ~~of~~ microbial decontamination of food;

- ~~microbial load in contaminated food at the point of consumption;~~

- survival capacity and spread ~~redistribution~~ of resistant micro-organisms during the food production process (including slaughtering, processing, storage, transportation and retailing);

- disposal practices for waste products and the opportunity for human exposure to resistant micro-organisms or resistance determinants in those waste products;

- ~~point of consumption of food (professional catering, home cooking);~~

- variation in consumption and food-handling methods of exposed populations and subgroups of the population;

- capacity of resistant micro-organisms to become established in humans;

- human-to-human transmission of the micro-organisms under consideration;

- capacity of resistant micro-organisms to transfer resistance to human commensal micro-organisms and zoonotic agents;

- amount and type of antimicrobials used in response to human illness;

- pharmacokinetics (such as metabolism, bioavailability and, access to intestinal flora).

5. Consequence assessment

A consequence assessment describes the relationship between specified exposures to resistant micro-organisms or resistance determinants and the consequences of those exposures. A causal process must exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of them occurring.

The following factors should be considered in the consequence assessment:

- microbial dose – host response relationships;

- variation in susceptibility of exposed populations or subgroups of the population;

- variation and frequency of human health effects resulting from loss of efficacy of antimicrobial agents and associated costs;

- potential linkage of virulence attributes and resistance;

- ~~changes in human medicinal practices resulting from reduced confidence in antimicrobials;~~

- changes in food consumption patterns due to loss of confidence in the safety of food products and any associated secondary *risks*;

- ~~associated costs;~~

- interference with first line/choice antimicrobial therapy in humans;

- importance of the antimicrobial agent in human medicine ~~perceived future usefulness of the antimicrobial (time reference)~~;

- prevalence of resistance in human bacterial pathogens under consideration.

6. Risk estimation

A *risk* estimation integrates the results from the release assessment, exposure assessment and consequence assessment to produce overall estimates of *risks* associated with the *hazards*. Thus, *risk* estimation takes into account the whole of the *risk* pathway from *hazard identification* to the unwanted consequences.

The following factors should be considered in the *risk* estimation:

- number of people falling ill and the proportion of that number affected with antimicrobial resistant ~~strains of~~ micro-organisms;

- adverse effects on vulnerable human sub-population (children, immuno-compromised persons, elderly, etc.);

- increased severity or duration of infectious *disease*;

- number of person~~/~~ or days of illness per year;

- deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population);

- ~~importance~~ severity of the ~~pathology~~ infection caused by the target micro-organisms;

- existence or absence of alternative antimicrobial therapy;

- potential impact of switching to an alternative antimicrobial agent (e.g. alternatives with potential increased toxicity);

- occurrence ~~incidence~~ of antimicrobial resistance in target pathogens observed in humans;

- consequences of the overall ~~to allow weighted summation of different~~ *risk* impacts (e.g. illness and hospitalisation).

7. Risk management components ~~options and risk communication~~

The OIE defines risk management as consisting of the steps described below. ~~Risk management options and risk communication have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.~~

a) Risk evaluation - the process of comparing the risk estimated in the risk assessment with the Member Country's appropriate level of protection.

b) Option evaluation.

A range of risk management options is available to minimise the emergence and spread of antimicrobial resistance and these include both regulatory and non-regulatory risk management options, such as the development of codes of practice concerning the use of antimicrobials in animal husbandry. Risk management decisions need to consider fully the implications of these different options for human health and animal health and welfare and also take into account economic considerations and any associated environmental issues. Effective control of certain bacterial diseases of animals will have the dual benefit of reducing the risks linked to antimicrobial resistance, in cases where the bacterial disease under consideration has also developed antimicrobial resistance.

c) Implementation

Risk managers should develop an implementation plan that describes how the decision will be implemented, by whom and when. National or regional authorities should ensure an appropriate regulatory framework and infrastructure.

d) Monitoring and review

Risk management options have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.

8. Risk communication

Communication with all interested parties should be promoted at the earliest opportunity and integrated into all phasis of a risk analysis. This will provide all interested parties, including risk managers, with the better understanding of risk management approaches. Risk communication should be well documented.

Article 6.10.3.

Analysis of risks to animal health

1. Definition of the risk

The *infection* of *animals* with micro-organisms that have acquired resistance to ~~from the use of~~ a specific antimicrobial agent~~(s)~~ due to its use in *animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal *infection*.

2. Hazard identification

- m~~M~~icro-organisms that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial agent(s) in *animals*.

- m~~M~~icro-organisms having obtained a resistance determinant(s) from other micro-organisms which have acquired resistance arising from the use of an antimicrobial agent(s) in *animals*.

The *identification of the hazard* must include considerations of the class or subclass of the antimicrobial agent(s). This definition should be read in conjunction with point 4) of Article 6.10.1.

3. Release assessment

The following factors should be considered in the release assessment:

- animal species treated with the antimicrobial agent in question;
- number of *animals* treated, sex, age and their geographical distribution;
- dosage regimen including ~~amounts used and~~ duration of ~~treatment~~ use;
- ~~variation in~~ methods and routes of administration of the antimicrobial agent(s);
- the pharmacokinetics or pharmacodynamics ~~/ pharmacokinetics~~ of the antimicrobial agent(s);
- site and type of *infection;*
- development of resistant micro-organisms;
- mechanisms and pathways of resistance transfer;
- cross-resistance ~~and/~~or co-resistance with other antimicrobial agents;
- data on occurrence of resistant micro-organisms through surveillance of animals, products of animal origin and animal waste products ~~for the existence of resistant micro-organisms~~.

4. Exposure assessment

The following factors should be considered in the exposure assessment:

- prevalence and trends of resistant micro-organisms in clinically ill and clinically unaffected *animals*;
- prevalence of resistant micro-organisms in feed / the animal environment;
- animal-to-animal transmission of the resistant micro-organisms (animal husbandry methods, movement of *animals*);
- number ~~/~~ or percentage of *animals* treated;
- ~~dissemination of resistant micro-organisms from *animals* (animal husbandry methods, movement of *animals*);~~
- quantity and trends of antimicrobial agent(s) used in *animals*;
- ~~treatment regimens (dose, route of administration, duration);~~
- survival capacity ~~of resistant micro-organisms~~ and spread of resistant micro-organsims;
- exposure of *wild-life* to resistant micro-organisms;
- disposal practices for waste products and the opportunity for animal exposure to resistant micro-organisms or resistance determinants in those products;

- capacity of resistant micro-organisms to become established in *animal*s ~~intestinal flora~~;
- exposure to resistance determinants from other sources such as water, effluent, waste pollution, etc.;
- ~~dose, route of administration and duration of treatment~~;
- pharmacokinetics, such as ~~(~~metabolism, bioavailability, access to intestinal flora~~)~~;
- transfer ~~cycling~~ of resistant micro-organisms between humans, animals and the environment.

5. Consequence assessment

The following factors should be considered in the consequence assessment:

- microbial dose – host response relationships;
- variation in disease susceptibility of exposed populations and subgroups of the populations;
- variation and frequency of animal health effects resulting from loss of efficacy of antimicrobial agents and associated costs;
- potential linkage of virulence attributes and resistance;
- ~~changes in practices resulting from reduced confidence in antimicrobials;~~
- ~~associated cost;~~
- ~~perceived future~~ importance~~usefulness~~ of the ~~drug~~ antimicrobial agent in animal health (see OIE list of antimicrobials of veterinary importance) ~~(time reference)~~.

6. Risk estimation

The following factors should be considered in the *risk* estimation:

- additional burden of disease due to antimicrobial resistant micro-organisms;
- number of therapeutic failures due to antimicrobial resistant micro-organisms;
- increased severity and duration of infectious disease;
- *animal welfare;*
- ~~economic cost;~~
- deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population);
- existence or absence of alternative antimicrobial therapy;
- potential impact of switching to an alternative antimicrobial agent e.g. alternatives with potential increased toxicity;
- estimation of the economic impact and cost on animal health and production.
- ~~incidence of resistance observed in *animals.*~~

7. Risk management ~~options~~components ~~and risk communication~~

The relevant provisions contained in Article 6.9.7. do apply.

~~Risk management options and risk communication have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.~~

~~The relevant recommendations (Articles 2.1.5., 2.1.6. and 2.1.7.) in the *Terrestrial Code* apply.~~

~~A range of *risk management* options is available to minimize the emergence and spread of antimicrobial resistance and these include both regulatory and non-regulatory *risk management* options, such as the development of codes of practice concerning the use of antimicrobials in animal husbandry. *Risk management* decisions need to consider fully the implications of these different options for human health and animal health and *welfare* and also take into account economic considerations and any associated environmental issues. Effective control of certain bacterial *diseases* of *animals* will have the dual benefit of reducing the *risks* linked to antimicrobial resistance, in cases where the bacterial *disease* under consideration has also developed antimicrobial resistance. Appropriate communication with all stakeholders is essential throughout the *risk assessment* process.~~

8. Risk communication

The relevant provisions contained in Article 6.9.8. do apply.