Annex XII

USA Comments (Please note: all recommended changes are indicated in blue text – both deletions (strike-through) and new text (double underlined))

CHAPTER 6.10.

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 microorganisms of animal origin

1. Introduction

Antimicrobial resistance is a naturally occuring phenomenon and the selection or dissemination of antimicrobial resistance can occur or be influenced by factors other than the use of antimicrobial agents.. However, ~~P~~problems related to antimicrobial resistance are inherently linked to *antimicrobial agent* use in any environment, including human and non-human usages. ~~However t~~The ~~selection emergence or dissemination of antimicrobial resistance can occur or be influenced by through factors other than the use of *antimicrobial agents*~~.

Rationale: Suggested change in sentence sequence for improved clarity and emphasis.

Antimicrobial resistance associated with the use of antimicrobial agents for therapeutic and ~~non-therapeutic~~ production purposes may lead to the selection and dissemination of antimicrobial resistant microorganisms. with a resulting loss of therapeutic efficacy in animal and human medicine of one or several *antimicrobial agents.*

Rationale: The definition of "non-therapeutic" can vary. The US Food and Drug Administration currently uses the term "production" to describe growth-promoting antimicrobials with label claims such as increased rate of gain or increased feed efficiency.

~~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 microorganisms. 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.~~

2. Objective

For the purpose of this chapter, the principal aim of *risk analysis*, ~~for the purpose of this chapter, for antimicrobial resistance in micro-organisms from *animals*~~ is to provide Members Countries with a transparent, objective and scientifically defensible method of assessing and managing the human and

animal health *risks* associated with the selection and dissemination ~~development~~ of resistance arising from the use of *antimicrobial agents* in *animals*.

Guidance on the issue of foodborne antimicrobial resistance related to the non-human use of *antimicrobial agents* is covered by the Codex Guidelines for risk analysis of foodborne antimicrobial resistance (CAC/GL77-2011).

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 assessment*, *risk management* and *risk communication*.

The chapter includes factors to be considered at various steps of the *risk analysis* process. These factors are not intended to be exhaustive and not all elements may be applicable in all situations.

~~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*~~ in Chapter 2.1.

For the purpose of this chapter, the *hazard* is the resistant microorganism 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-organisms to another~~ potential for resistant microorganisms to cause adverse health effects, as well as the potential for horizontal transfer of genetic determinants between microorganisms. The conditions under which the *hazard* might produce adverse consequences include any scenarios through which humans or *animals* could become exposed to an antimicrobial resistant 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 microorganisms resulting from the use of *antimicrobial agents* in *animals* should examine:

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

b) consideration of all pathways and their importance, by which humans and *animals* could be exposed to these resistant microorganisms 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 principles of *risk assessment* as defined in Chapter 2.1. of the *Terrestrial Code* applyies equally to both *qualitative* and *quantitative risk assessment*. At a minimum, a *qualitative risk assessment* should always be undertaken.~~

Rationale: 1) Grammar; and 2) The United States proposes deleting this last sentence as it is too prescriptive and does not contribute to a better understanding of the process or the chapter.

Article 6.10.2.

Analysis of risks to human health

1. Definition of the risk

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

2. Hazard identification

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

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

The identification of the *hazard* ~~must~~ should 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

General observation: OIE Code Chapter 2.1 was recently modified to change the term 'release assessment' with 'entry assessment'. If consistency with Chapter 2.1 is desired, then the Code Commission may want to consider making the same modification herein.

A release assessment describes the biological pathways ~~necessary~~ that may ~~to~~ lead to the release of resistant microorganisms or resistance determinants into a particular environment due to ~~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,~~. It also estimates ~~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:

- animal species, category such as food producing, zoo or companion animal, and, where appropriate, production type ~~(e.g.~~ such as veal calves or dairy cattle, broilers or laying hens~~)~~, ~~of animal~~ treated with the *antimicrobial agent*~~(s)~~ in question;

- number of *animals* treated~~,~~ ~~sex,~~ and their age, ~~and their~~ geographical distribution, and where appropriate, sex; ~~of those *animals*~~;

Rationale: The United States recommends the suggested text as shown because it is unclear how sex is relevant to the release assessment

- prevalence of *infection* or *disease* for which the *antimicrobial agent* is indicated in the target animal population;

- data on trends in *antimicrobial agent* use, including extra-label and off-label use; ~~and changes in farm production systems;~~

~~- data on potential extra-label or off-label use;~~

Rationale: extra- and off-label uses are two of the possible ways in which antimicrobial agents can be used. As such, we recommend combining the fourth and fifth bullet points into one factor to be considered in the release assessment. In addition, production systems have not been shown to have a correlation with antimicrobial use, so we recommend deleting it. At the very least, "changes in farm production systems" should be moved to a separate bullet so that it becomes a separate factor to be considered in release assessment as opposed to a factor seemingly correlated with trends in use of antimicrobials.

- ~~variation in~~ methods and routes of administration of the *antimicrobial agent~~(s)~~*;
- dosage regimen (dose, dosing interval and duration of the treatment) ~~including duration of use~~;
- ~~the~~ pharmacokinetics and relevant ~~or~~ pharmacodynamics~~/pharmacokinetics~~ of the *antimicrobial agent~~(s)~~*;
- ~~micro-organisms developing resistance as a result of the antimicrobial(s) use~~ prevalence of pathogens that are likely to develop ~~acquire~~ resistance in animal species ~~host~~;

Rationale: as originally written, it suggests the interest is in the pathogen load within particular animals, rather than the percentage of animals carrying the pathogen across a population.

- prevalence of 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 trends and occurrence of resistant microorganisms obtained 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 microorganisms or resistance determinants released from a given antimicrobial use in *animals*, and estimat~~es~~~~ing~~ the probability of the exposures occurring. The ~~probability~~ likelihood of exposure to the identified *hazards* is estimated for specified exposure conditions with respect to amounts, timing, frequency, duration of exposure, routes of exposur ~~and the number~~, species and other characteristics of the human populations exposed.

Rationale: The term 'Probability' implies a quantitative estimate of the event occurring. The term 'likelihood' is used in other parts of the chapter and applies to both quantitative and qualitative risk assessments. Therefore, we recommend changing the term throughout the chapter.

The following factors should be considered in the exposure assessment:

- human demographics, including population subgroups, and food consumption patterns, including traditions and cultural practices ~~in~~ with respect to the preparation and storage of food;

Rationale: Grammar

- prevalence of resistant microorganisms in food at the point of consumption or other exposure;
- microbial load in contaminated food at the point of consumption or ~~other~~ exposure ~~for quantitative risk assessment~~;

Rationale: Unless the term "other exposure" is defined it does not appear needed, because known exposures such as "at the point of consumption" and "in the environment" are already included as factors to be considered.

- environmental contamination with resistant microorganisms;

- occurrence of resistant microorganisms in animal feed that have the capacity to become established in the animals, thus leading to contamination of foods of animal origin; ~~prevalence of animal feed contaminated with resistant micro-organisms~~;

Rationale: The United States suggests the added clarifying text because there is no pathway for human exposure from resistant microorganisms in animal feed unless the animal becomes colonized with the microorganisms, thus potentially and subsequently contaminating the food supply.

- transfer ~~cycling~~ of resistant microorganisms and their resistance determinants 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 dissemination ~~spread~~ ~~redistribution~~ of resistant microorganisms during the food production process (including slaughtering, processing, storage, transportation and retailing);

- disposal practices for **waste** products and the likelihood ~~opportunity~~ for human exposure to resistant microorganisms or resistance determinants ~~in~~ through those waste products;

Comment: Does the term "waste" referred to above, "animal waste", or does it refer to "food waste"? Clarity to this term should be provided.

- ~~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 microorganisms to become established in humans;

- human-to-human transmission of the microorganisms under consideration;

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

- amount and type of *antimicrobial agents* used ~~in response~~ to treat humans ~~illness~~;

- pharmacokinetics~~.~~ ~~(~~such as metabolism, bioavailability and distribution to the gastrointestinal ~~access to intestinal~~ flora.

5. Consequence assessment

A consequence assessment describes the relationship between specified exposures to resistant microorganisms or resistance determinants and the consequences of those exposures. A causal process ~~must~~ should 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~~ likelihood of them occurring.

Rationale: The term 'Probability' implies a quantitative estimate of the event occurring. The term 'likelihood' is used in other parts of the chapter and applies to both quantitative and qualitative risk assessments. Therefore, we recommend changing the term throughout the chapter.

The following factors should be considered in the consequence assessment:

- microbial dose ~~– host response relationships~~ and subsequent host response interactions;

Rationale: The OIE proposed wording as written seems vague. The United States suggests re-writing using the text as indicated.

- 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 or /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.
- number of people falling ill and the proportion of that number infected ~~affected~~ with antimicrobial resistant ~~strains of~~ microorganisms;
- adverse effects on vulnerable human sub-population (children, immunocompromised 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~~ reduced life expectancy for a random member of the population or a member of a specific ~~more exposed~~ sub-population) linked to antimicrobial resistant microorganisms when compared with deaths linked to sensitive microorganisms of the same species;

Rationale: Note: since we are making a suggested change in a section we have proposed to move, we are indicating that change in green highlight. This point as written is unclear. Specifically, the terms "lifetime" and "more exposed sub-population" are what make the phrase unclear. The suggested (highlighted) edits help clarify this sentence. In addition (also highlighted and double underlined), the factor to be considered here is the risk of human death due to infection with microorganisms that have become resistant to antimicrobials as a result of selective pressures from use of antimicrobial agents in animals. Thus, the risk estimation is incomplete without a comparison to the risk of death due to infection with a sensitive microorganism of the same species.

- ~~importance~~ severity of the ~~pathology~~ *disease* ~~infection~~ caused by the target resistant microorganisms;

Rationale: There is potential for differing risks of disease caused by a resistant vs a sensitive microorganism, and therefore the severity of disease caused by the resistant organism should be used for risk estimation.

- availability ~~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).

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.

For a quantitative assessment, the final outputs may include:

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

- estimated numbers of *herds*, *flocks*, *animals* or people likely to experience health impacts of various degrees of severity over time;
- probability distributions, confidence intervals, and other means for expressing the uncertainties in these estimates;
- portrayal of the variance of all model inputs;
- a sensitivity analysis to rank the inputs as to their contribution to the variance of the *risk* estimation output;
- analysis of the dependence and correlation between model inputs.

For a qualitative assessment, the final outputs may include a categorical descriptor of the likelihood of entry, exposure and consequence assessments and an overall risk ranking. The supporting rationale for assigning a categorical descriptor should be provided.

- ~~number of people falling ill and the proportion of that number infected affected with antimicrobial resistant strains of microorganisms;~~
- ~~adverse effects on vulnerable human sub-population (children, immunocompromised 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) linked to antimicrobial resistant microorganisms;~~
- ~~importance severity of the pathology *disease* infection caused by the target microorganisms;~~
- ~~availability 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).~~

Rationale: The list of factors for consideration is really part of consequence assessment. Therefore, the United States proposes moving the existing list under Articles 6.10.2.5 and 6.10.3.6 to Articles 6.10.2.5 and 6.10.3.5 respectively; and replaces that list with the suggested test indicated.

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 dissemination ~~spread~~ of antimicrobial resistance and these include both regulatory and non-regulatory ~~risk management~~ options, such as the development of codes of practice ~~concerning~~ for the use of *antimicrobial agents* 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~~ *animal* diseases ~~of *animals* will~~ can have the dual benefits of reducing ~~the~~ risks to human health ~~linked to~~ associated with both bacterial contamination of carcasses and antimicrobial resistance, ~~in cases where the bacterial disease pathogen under consideration has also developed antimicrobial resistance~~.

Rationale: Control of animal disease can reduce contamination of the carcass with both susceptible and resistant microorganisms, thereby reducing risks to human health. Additionally, control of animal disease can also minimize the need for use of antimicrobials, further reducing selection and dissemination of 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~~ *Competent Authorities* should ensure an appropriate regulatory framework and infrastructure.

d) Monitoring and review

Risk management options ~~have to~~ should 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 phases 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 also well documented.

Article 6.10.3.

Analysis of risks to animal health

1. Definition of the risk

The *infection* of *animals* with microorganisms that have acquired resistance ~~to~~ ~~from the use of~~ ~~a specific *antimicrobial agent*(s)~~ due to ~~the~~ antimicrobial usage ~~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~~icroorganisms that have acquired resistance, (including multiple resistance) arising from the use of an *antimicrobial agent~~(s)~~* in *animals*;

- m~~M~~icroorganisms having obtained a resistance determinant~~(s)~~ from another microorganism~~s~~ which has~~ve~~ acquired resistance arising from the use of an *antimicrobial agent~~(s)~~* in *animals*.

The *identification of the hazard* ~~must~~ should 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, category such as food producing, zoo or companion animal and, where appropriate, production type, ~~(e.g. such as~~ veal calves or dairy cattle, broilers or laying hens~~)~~ treated with the *antimicrobial agent~~(s)~~* in question;

- number of *animals* treated, sex, age and their geographical distribution;

- prevalence of *infection* or *disease* for which the *antimicrobial agent* is indicated in the target animal population;

- data on trends in *antimicrobial agent* use including extra-label or off-label use ~~and changes in farm production systems~~;

- ~~potential extra-label or off-label use~~;

Rationale: extra- and off-label uses are two of the possible ways in which antimicrobial agents can be used. As such, we recommend combining the fourth and fifth bullet points into one factor to be considered in the release assessment. In addition, production systems have not been shown to have a correlation with antimicrobial use, so we recommend deleting it. At the very least, "changes in farm production systems" should be moved to a separate bullet so that it becomes a separate factor to be considered in release assessment as opposed to a factor seemingly correlated with trends in use of antimicrobials

- 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~~ and relevant pharmacodynamics~~/ pharmacokinetics~~ of the *antimicrobial agent~~(s)~~*;

- site and type of *infection;*

- development of resistant microorganisms;

- mechanisms and pathways of resistance transfer;

- cross-resistance ~~and/~~or co-resistance with other *antimicrobial agents*;

- data on trends and occurrence of resistant microorganisms obtained 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 microorganisms in clinically ill and clinically unaffected *animals*;
- occurrence ~~prevalence~~ of resistant microorganisms in feed and in~~/~~ the animal environment;
- animal-to-animal transmission of the resistant microorganisms and their resistance determinants (animal husbandry practices ~~methods~~ and 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 dissemination ~~spread~~ of resistant microorganisms;
- exposure of *wildlife* to resistant microorganisms;
- disposal practices for waste products and the likelihood ~~opportunity~~ for animal exposure to resistant microorganisms or resistance determinants ~~in~~through those products;
- capacity of resistant microorganisms to become established in *animals* ~~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, distribution to the gastrointestinal flora ~~access to intestinal flora~~;
- transfer ~~cycling~~ of resistant microorganisms and their resistance determinants between humans, *animals* and the environment.

5. Consequence assessment

The following factors should be considered in the consequence assessment:

- microbial dose ~~- host response relationships~~ and subsequent host response interactions;

Rationale: The OIE proposed wording as written seems vague. The United States suggests re-writing using the text as indicated.

- 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 *antimicrobial agents* of veterinary importance) ~~(time reference)~~.
- additional burden of *disease* due to antimicrobial resistant microorganisms;

- number of therapeutic failures due to antimicrobial resistant microorganisms;
- increased severity and duration of infectious *disease*;
- impact on *animal welfare;*
- estimation of the economic impact and cost on animal health and production;
- ~~economic cost;~~
- deaths (total per year; probability per year or ~~lifetime~~ reduced life expectancy for a random member of the population or a member of a specific ~~more exposed~~ sub-population) linked to antimicrobial resistant microorganisms when compared with deaths linked to sensitive microorganisms of the same species;

Rationale: Note: since we are making a suggested change in a section we have proposed to move, we are indicating that change in green highlight. This point as written is unclear. Specifically, the terms "lifetime" and "more exposed sub-population" are what make the phrase unclear. The suggested (highlighted) edits help clarify this sentence. In addition (also highlighted and double underlined), the factor to be considered here is the risk of human death due to infection with microorganisms that have become resistant to antimicrobials as a result of selective pressures from use of antimicrobial agents in animals. Thus, the risk estimation is incomplete without a comparison to the risk of death due to infection with a sensitive microorganism of the same species.

- availability ~~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*.~~

6. Risk estimation

For a quantitative assessment, the final outputs may include:

- estimated numbers of *herds*, *flocks*, *animals* or people likely to experience health impacts of various degrees of severity over time;
- probability distributions, confidence intervals, and other means for expressing the uncertainties in these estimates;
- portrayal of the variance of all model inputs;
- a sensitivity analysis to rank the inputs as to their contribution to the variance of the *risk* estimation output;
- analysis of the dependence and correlation between model inputs.

For a qualitative assessment, the final outputs may include a categorical descriptor of the likelihood of entry, exposure and consequence assessments and an overall risk ranking. The supporting rationale for assigning a categorical descriptor should be provided.

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

- additional burden of *disease* due to antimicrobial resistant microorganisms;
- number of therapeutic failures due to antimicrobial resistant microorganisms;
- increased severity and duration of infectious *disease*;
- impact on *animal welfare;*
- estimation of the economic impact and cost on animal health and production;
- 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) linked to antimicrobial resistant microorganisms;
- availability existence or absence of alternative antimicrobial therapy;
- potential impact of switching to an alternative *antimicrobial agent*, e.g. alternatives with potential increased toxicity[1].
- estimation of the economic impact and cost on animal health and production.
- incidence of resistance observed in *animals*.

Rationale: The list of factors for consideration is really part of consequence assessment. Therefore, the United States proposes moving the existing list under Articles 6.10.2.5 and 6.10.3.6 to Articles 6.10.2.5 and 6.10.3.5 respectively; and replaces that list with the suggested test indicated.

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

The relevant provisions ~~contained~~ in point 7 of Article ~~6.9.7.~~ 6.10.2. ~~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 point 8 of Article ~~6.9.8.~~ 6.10.2. ~~do~~ apply.

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