CHAPTER 6.10.

RISK ASSESSMENT FOR ANTIMICROBIAL RESISTANCE ARISING FROM THE USE OF ANTIMICROBIALS IN ANIMALS

Article 6.10.1.

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

1. Introduction

The use of antimicrobials for therapy, 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 drugs and includes the emergence of multi-resistant micro-organisms.

2. Objective

The principal aim of *risk analysis* for antimicrobial resistance in micro-organisms from *animals* is to provide Member Countries 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 antimicrobials in *animals*.

3. The risk analysis process

The principles of *risk analysis* are described in Section 2 of this *Terrestrial Code*.

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

For the purposes of this chapter, the *hazard* is the resistance determinant that emerges as a result of the use of a specific antimicrobial 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. 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 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, 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 of exposure;

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

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 used 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(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(s) in *animals*.

The *identification of the hazard* must include consideration of the class or subclass of the antimicrobial(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 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(s) in question;

– number of *animals* treated, geographical distribution of those *animals*;

– variation in methods and routes of administration of the antimicrobial(s);

– the pharmacodynamics/pharmacokinetics of the antimicrobial(s);

– micro-organisms developing resistance as a result of the antimicrobial(s) use;

– mechanism of direct or indirect transfer of resistance;

– cross-resistance and/or co-resistance with other antimicrobials;

– 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;

– prevalence of resistant micro-organisms in food;

– environmental contamination with resistant micro-organisms;

– prevalence of animal feed contaminated with resistant micro-organisms;

– cycling of resistant micro-organisms between humans, *animals* and the environment;

– steps of microbial decontamination of food;

– microbial load in contaminated food at the point of consumption;

– survival capacity and 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 (metabolism, bioavailability, 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:

– dose-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 antimicrobials;
– 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;
– 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 resistant strains of micro-organisms;
– increased severity or duration of infectious *disease*;
– number of person/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 of the pathology caused by the target micro-organisms;
– absence of alternate antimicrobial therapy;
– incidence of resistance observed in humans;
– consequences to allow weighted summation of different *risk* impacts (e.g. illness and hospitalisation).

7. Risk management options and risk communication

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

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 from the use of a specific antimicrobial(s) in *animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal *infection*.

2. Hazard identification

– Micro-organisms that have acquired resistance (including multiple resistance) arising from the use of an antimicrobial(s) in *animals*.
– Micro-organisms having obtained a resistance determinant(s) from another micro-organisms which have acquired resistance arising from the use of an antimicrobial(s) in *animals*.

The *identification of the hazard* must include considerations of the class or subclass of the antimicrobial(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;
- number of *animals* treated, sex, age and their geographical distribution;
- amounts used and duration of treatment;
- variation in methods and routes of administration of the antimicrobial(s);
- the pharmacodynamics/ pharmacokinetics of the antimicrobial(s);
- site and type of *infection*;
- development of resistant micro-organisms;
- mechanisms and pathways of resistance transfer;
- cross-resistance and/or co-resistance;
- 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;
- number/percentage of *animals* treated;
- dissemination of resistant micro-organisms from *animals* (animal husbandry methods, movement of *animals*);
- quantity of antimicrobial(s) used in *animals*;
- treatment regimens (dose, route of administration, duration);
- survival capacity of resistant micro-organisms;
- exposure of *wildlife* 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 intestinal flora;
- exposure to resistance determinants from other sources;
- dose, route of administration and duration of treatment;
- pharmacokinetics (metabolism, bioavailability, access to intestinal flora);
- cycling of resistant micro-organisms between humans, *animals* and the environment.

5. Consequence assessment

The following factors should be considered in the consequence assessment:

- dose-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 antimicrobials;
- changes in practices resulting from reduced confidence in antimicrobials;
- associated cost;
- perceived future usefulness of the drug (time reference).

6. Risk estimation

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

- number of therapeutic failures due to resistant micro-organisms;
- *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);
- incidence of resistance observed in *animals*.

7. Risk management options and risk communication

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.