資料４

家畜等への抗菌性物質の使用により選択される薬剤耐性菌の食品健康影響に関する評価指針改訂の検討について

１．背景

「家畜等への抗菌性物質の使用により選択される薬剤耐性菌の食品健康影響に関する評価指針」（平成 16 年９月 30 日食品安全委員会決定）（以下「評価指針」という。）については、薬剤耐性（AMR）対策アクションプランに係る食品安全委員会行動計画 2016-2020（2017 年３月 28 日食品安全委員会決定）において必要に応じて見直しを行うこととなっており、国際的な動向を踏まえたより適切な評価を推進するため、改訂する運びとなった。評価指針の改訂については、2020 年度の食品安全委員会運営計画に明記されており、2021 年度の食品安全委員会運営計画においても、当該評価指針の改訂を引き続き検討することが明記されている。

薬剤耐性菌 WG は、2021 年３月８日に開催された第 31 回会合において、評価指針改訂作業に着手をしたところ。第 31 回薬剤耐性菌 WG では、評価指針を①国際動向、②2003 年以降に得られた知見、③水産動物の評価の 3 つ大きな要素についてそれぞれ審議し、1 年かけて改訂する方針を確認した。

２．第 32 回薬剤耐性菌 WG における審議

国際動向を評価指針に反映する作業を行う。具体的には、初版作成時に参照をした（別紙１参照）、以下の国際機関又は主要国／地域（以下「国際機関等」という。）の作成したガイドライン等と評価指針を比較し、評価指針に不足している記載を盛り込む。

- Codex Alimentarius Commission
  Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CAC/GL 77-2011)
- OIE
  Chapter 6.11 Risk Analysis for Antimicrobial Resistance Arising from the Use of Antimicrobial Agents in Animals
- VICH
  VICH GL27 Guidance on Pre-approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance
- 米国
  Guidance for Industry Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern
- EU
  Guideline on the Assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing

animals (Draft2)

- オーストラリア
  Antibiotic resistance risk assessments（HP 掲載）

３．2004 年９月以降の動向

国際動向を踏まえて評価指針を改定するに当たっては、特に評価指針作成の際に考慮に入れていない、2004 年９月以降に発生した以下のイベントに留意する。

（１）Codex Alimentarius Commission
2011 年に上記ガイドラインを新規採択。

（２）OIE
2005 年から 2015 年にかけて複数回改正が行われている。一番大きな改正が行われたのは 2014 年であり、多くの文言の修正が行われているが、構成に変更はない。（別紙２参照）

（３）EU
2018 年に上記ガイドライン案を公表。まだ草案であり完成はしていない。

（４）米国及び VICH
2004 年９月以降変更なし。

（５）オーストラリア
HP に掲載されている情報であり、改正の時期及びその概要等の詳細不明。

４．留意事項

- 評価指針に改訂があった場合は、過去の評価の取り扱いについて検討する必要。
- リスク管理機関と相談をしながら進める必要。
- 評価指針に記載した内容に沿って評価書が作成されることに留意。

５．今後のスケジュール

６月 11 日を含めて 12 月までに計 5 回の WG[1]を開催し審議完了を目指す。

次回（７月を予定）は再度国際動向について審議する予定（「食品を介してヒトの健康に影響を及ぼす細菌に対する抗菌性物質の重要度のランク付け」（平成 18 年４月 13 日食品安全委員会決定）の改正の必要性についても審議予定）。

６．結論及び推奨事項

資料５及び資料６に、国際機関等のガイドラインと評価指針の記載を比較した表及びその結果をまとめた。今回の WG では、資料５及び６の内容を踏まえ、評価指針案（資料７）について審議願いたい。

[1] ６月 11 日、７月、９月、残り 10 月～12 月に２回を開催予定

（別紙１）

「家畜等への抗菌性物質の使用により選択される薬剤耐性菌の食品健康影響に関する評価指針」作成に係る経緯

2003 年 12 月８日に農林水産大臣より薬剤耐性菌に係る食品健康影響評価の要請がなされたことを受け、食品安全委員会は、肥料飼料等専門調査会、動物用医薬品専門調査会及び微生物専門調査会よりなる合同専門調査会を 2004 年 2 月から 9 月にかけて計 5 回開催し、評価方針案を作成した。

座長は、当時の肥料飼料等専門調査会の座長であった唐木英明氏が務め、荒川専門委員及び池専門参考人を含む計 11 名の専門委員及び専門参考人が作成に参加した。

第 1 回合同専門調査会では、評価指針案をドラフトする 4 名の起草委員が指名され、農林水産省が当時作成していた「家畜等への抗菌性飼料添加物使用が公衆衛生に及ぼす抗菌剤耐性リスクの評価法に関する指針」や OIE コードをベースに、その他の国際機関や主要国／地域のガイドラインを参照しながら評価指針案を作成した。

当時 EU はまだガイドラインを示していなかったため、実際の評価を元にケーススタディを実施している。

その後パブリックコメントの募集そして意見交換会を経て、2004 年 9 月に食品安全委員会に報告し、決定となった。

【経緯】

2004 年 2 月 13 日：合同専門調査会、評価指針の作成方針決定
2004 年 3 月 29 日：合同専門調査会、評価書案の審議
2004 年 4 月 28 日：合同専門調査会、評価書案の審議
2004 年 6 月 23 日：合同専門調査会、評価書案の審議
2004 年 7 月 8 日～8 月 4 日：パブリックコメント（計 14 通）
2004 年 8 月 2 日　：評価指針案に関する意見交換会（東京）
2004 年 9 月 15 日：合同専門調査会、意見・情報の募集結果の審議
2004 年 9 月 30 日：食品安全委員会にて決定

【委員及び専門参考人】

唐木　英明　（座長）	寺門　誠致　（起草委員）	三森　国敏
荒川　宜親　（起草委員）	青木　宙	中村　政幸
井上　松久　（起草委員）	池　康嘉	渡邉　治雄
嶋田　甚五郎（起草委員）	岡部　信彦	

【参照したガイドライン等】

（合同調査会にて参考資料として配られたもの）

- 農林水産省「家畜等への抗菌性飼料添加物使用が公衆衛生に及ぼす抗菌剤耐性リスクの評価法に関する指針」
- OIE, “Scientific and Technical Review vol.20[3], December 2001, 797-870”
- OIE International Standards on Antimicrobial Resistance, 2003.
  (事務局注：当時 OIE は Ad hoc グループにおいてコード案を製作中であり、合同調査会はその作成中のコード案を参照していた。)
- FDA/CVM, “Guidance for Industry #152 (October 23, 2003)”
- Codex, “Principle and Guidelines for the Conduct of Microbiological Risk Assessment CAC/GL-30”
- VICH, “Guidance on Pre-approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance”

（評価指針の参照文献としてリストされているもの（上記を除く）

- 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.
- Part 10 of Veterinary Requirement Series, Submission to working party on antibiotics, National Registration Authority for Agricultural and Veterinary Chemicals, Australia, June 2000.
- 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.
- 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.
- The Reconsideration of the Registration of Products Containing Virginiamycin and Their Labels (Draft Review Report), March 2003, Australian Pesticides & Veterinary Medicines Authority.
- 論争の発生:抗生物質成長促進剤と公衆衛生 ヒトの健康と抗生物質成長促進－リスクの再評価－, HAN（FEFANA）.

【ケーススタディ】

EMEA 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

（別紙２）

Annex XV

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 tThe selection emergence or dissemination of antimicrobial resistance can occur or be influenced by through factors other than the use of *antimicrobial agents*.~~

Antimicrobial resistance associated with the use of *antimicrobial agents* for therapeutic and non-therapeutic 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*.

~~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 Member~~s~~ 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 food-borne antimicrobial resistance related to the non-human use of *antimicrobial agents* is covered by the Codex Guidelines for risk analysis of food-borne 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*.

Annex XV (contd)

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*~~ apply~~ies~~ 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 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

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, entertainment 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*~~;
- 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;
- data on ~~potential~~ extra-label or off-label use;
- ~~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 an animal species ~~host~~;
- 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 estimates~~ing~~ 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.

Annex XV (contd)

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

The following factors should be considered in the consequence assessment:

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

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 infected ~~affected~~ with antimicrobial resistant ~~strains of~~ microorganisms;
- adverse effects on vulnerable human sub-population (children, immunocompromised persons, elderly, pregnant, 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 reduced life expectancy ~~lifetime~~ 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;
- ~~importance~~ severity of the ~~pathology~~ *disease* ~~infection~~ caused by the target resistant microorganisms;
- availability and cost ~~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).

Annex XV (contd)

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 reduction in *risk* expected from the proposed *risk management* measures ~~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 *animal* ~~certain bacterial~~ *diseases* ~~of animals~~ ~~will~~ can have the dual benefits of reducing ~~the~~ *risks* to human health ~~linked to~~ associated with both the bacterial pathogen under consideration and antimicrobial resistance~~, in cases where the bacterial disease pathogen 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~~ *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

- Microorganisms 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, entertainment 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~~, and their age~~, and their~~ geographical distribution and, where appropriate, sex;
- 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;
- data on ~~potential~~ extra-label or off-label use;
- dosage regimen (dose, dosing interval and duration of the treatment) ~~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*;

Annex XV (contd)

- ~~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~~ of 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;
- 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)~~.

6. Risk estimation

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~~ 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;

- availability and cost ~~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 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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— Text deleted