



Health
Canada Santé
Canada

**Veterinary Drugs Directorate
Health Products and Food Branch**

June 04, 2005

**Current Thinking on Risk Management Measures to Address
Antimicrobial Resistance Associated with the Use of Antimicrobial
Agents in Food-Producing Animals**

*Prepared for Consultation with Health Canada's Expert Advisory Committee on Antimicrobial
Resistance (AMR) Risk Assessment*

CONTENTS

I.	BACKGROUND AND ISSUE ANALYSIS	<u>3</u>
II.	CONSULTATIONS	<u>4</u>
III.	CONSIDERATIONS	<u>7</u>
IV.	RISK ASSESSMENT AND MANAGEMENT APPROACHES	<u>7</u>
V.	PROPOSED RISK ASSESSMENT POLICY FRAMEWORK	<u>9</u>
VI.	ACTION PLAN FOR AMR RISK ANALYSIS FOR VETERINARY ANTIMICROBIALS	<u>13</u>
VII.	GUIDANCE DOCUMENT FOR MICROBIOLOGICAL SAFETY STUDIES REQUIREMENTS FOR PREPARATION OF VETERINARY NEW DRUG SUBMISSIONS	<u>23</u>
VIII.	PROPOSED CATEGORIZATION OF ANTIMICROBIAL DRUGS	<u>31</u>
IX.	EXPERT ADVISORY COMMITTEE ON ANTIMICROBIAL RESISTANCE RISK ASSESSMENT	<u>34</u>
X.	TERMS OF REFERENCE OF THE INTERDEPARTMENTAL AMR SCIENCE COMMITTEE	<u>38</u>
XI.	TERMS OF REFERENCE OF THE INTERDEPARTMENTAL AMR POLICY COMMITTEE	<u>39</u>

I. BACKGROUND AND ISSUE ANALYSIS

The increasing emergence of bacterial pathogens resistant to currently available antimicrobial agents continues to drive multi-lateral international efforts to address the issue of antimicrobial resistance as a major public health and food safety issue. While it is recognized that medical uses of antimicrobial agents represent a major risk factor for AMR in humans, accumulating evidence indicates that the use of antimicrobial agents in veterinary medicine and livestock production is also an important contributing factor in the emergence of resistant bacteria and dissemination of resistant bacteria/resistance genes. The spread of resistance traits from animals to humans necessitates the assessment of human health risks associated with antimicrobial use in food-producing animals. Therefore, in recent years, attention has been focussed on the use of antimicrobial agents in food-producing animals and impacts on the development of AMR especially in clinically important bacterial pathogens.

The policy development process on AMR was initiated in recognition of the policy gaps within Health Canada to guide pre-approval assessment of new veterinary antimicrobial drugs, as well as post approval monitoring of antimicrobial agents. In the summer of 1997, Health Canada co-sponsored a consensus conference entitled "Controlling Antimicrobial Resistance: An Integrated Action Plan for Canadians". This conference identified a number of issues around AMR that should be tackled and considered in the development of a National Action Plan on AMR. A key result of this conference is the recognition that AMR is a multi-faceted issue, the management of which requires integrated strategies.

Health Canada in conjunction with the Ontario Ministry of Agriculture, Food and Rural Affairs co-sponsored the October 1999 conference on "Agriculture's Role in Managing Antimicrobial Resistance". This meeting provided a forum for discussion amongst stakeholders towards building a future strategy. In December 1999, a multi-stakeholder "*Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health*" was formed to provide advice to Health Canada on the development of antimicrobial use policies, surveillance and research related to the use of antimicrobial drugs in food-producing animals.

In June 2002, the Advisory Committee presented its final Report containing 38 recommendations to Health Canada. Following the publication of the Report of the Health Canada's *Advisory Committee on Animal Uses of Antimicrobial Agents and Impact on Resistance and Human Health*, steps have been made by Health Canada to address the issues raised in the AMR Report. The completion of the work of the Advisory Committee and the presentation of the Committee's final report to Health Canada represents a significant stride in understanding and addressing the AMR issue from a Canadian perspective.

In December, 2002, Health Canada's proposed response to the AMR Report was posted on the VDD's web site, along with the Issue Identification Paper prepared by the interdepartmental AMR Policy and Science Committees. The Issue Identification Paper elaborates on various issues that need to be considered in the policy development process. In conformity with the

requirements of Health Canada's Decision-Making Framework, stakeholders were given the opportunity to provide comments on the proposed response to each of the 38 recommendations of the Advisory Committee.

Consultation meetings were also held with Provincial/Territorial partners and with stakeholders in February 2003 and May 2003 respectively. Discussions were held on the ramifications of the regulation and distribution of antimicrobial drugs, the management of antimicrobial resistance risks, antimicrobial growth promotants, AMR surveillance, prudent use of antimicrobial agents, as well as research and education. On the basis of these consultation meetings as well as in consideration of a variety of risk management options, this Issue Analysis Summary is prepared to serve as the basis for developing risk management strategies on AMR as it relates to the use of antimicrobial agents in food-producing animals.

II. CONSULTATIONS

Consultation on this issue started with the official release on the VDD website of the Report of the AMR Advisory Committee in September 2002. E-mails and "AMR Bulletins" were sent to all stakeholders to notify them of the release of the publication as well as Health Canada's request for comments on the Report. In December 31, 2003, Health Canada's proposed responses to the recommendations were posted on the VDD Web site for another round of consultation. The consultation period was completed on February 15, 2003.

A formal consultation was held with the provinces/territories on February 7, 2003 to discuss recommendations requiring multi-jurisdictional involvement. A key objective of this consultation was to develop a common understanding of both federal and provincial initiatives on AMR. Provincial representatives were asked to prepare brief overviews of their respective provincial activities.

The following stakeholders were mailed hard copies of the Advisory Committee Report and were asked to provide comments:

Alberta Cattle Feeders' Association
Animal Nutrition Association of Canada
Association des vétérinaires en industrie animale du Québec
Canadian Animal Health Coalition
Canadian Animal Health Institute
Canadian Aquaculture Industry Alliance
Canadian Cattlemen's Association
Canadian Committee on Antibiotic Resistance
Canadian Egg Marketing Agency
Canadian On-Farm Food Safety Working Group
Canadian Pork Council

Canadian Poultry and Egg Processors Council
Canadian Public Health Association
Canadian Sheep Federation
Canadian Veterinary Medical Association
Chicken Farmers of Canada
College of Veterinarians
Consumers Association of Canada
Dairy Farmers of Canada
Environmental Defense Canada
Innofeed
Maple Leaf Foods Inc.
Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec
Nonprescription Drug Manufacturers Association of Canada (NDMAC)
Ordre des Médecins Vétérinaires du Québec
Ontario Ministry of Agriculture and Food
Ontario Pork Industry Council
Ontario Veterinary Medical Association
Pharmacia Animal Health
Alberta Veterinary Medical Association
Western Canadian Association of Bovine Practitioners

The following federal departments or agencies and program areas were also mailed hard copies of the AMR Report and were asked to provide comments on the Report as well as Health Canada's proposed responses:

Laboratory for Foodborne Zoonosis, PPHB, Health Canada
Centre for Infectious Disease Prevention and Control, PPHB, Health Canada
National Microbiology Laboratory, Winnipeg
Pest Management Regulatory Agency, Health Canada
Canadian Food Inspection Agency
Agriculture and Agri-Food Canada
Fisheries and Oceans Canada

In September 2003, an information gathering meeting was held with a representative of Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec (MAPAQ) on the regulation and distribution of antimicrobial drugs in Quebec, and to have an understanding of the status and impact of the prescription status regulation in Quebec.

Despite the complexity of the AMR issue, there are several areas of agreement among stakeholders. It is incontestable that there are significant science gaps regarding AMR but there is a clear understanding of the fundamental issues around AMR. Regulatory agencies and stakeholders agree with the need to minimize the risk associated with the development of AMR. Within the purview of a risk management strategy, stakeholders understand the rationale for

many of the recommendations of the Advisory Committee.

General Comments from Stakeholders

- Stakeholders were very appreciative of the process established by Health Canada to address the issue of antimicrobial resistance associated with the use of antimicrobial agents in food-producing animals.
- Health Canada should establish priorities and provide time frames for implementation of the recommendations.
- Health Canada is encouraged to exert greater controls over antimicrobial use in food-producing animals.

Specific Comments from Stakeholders:

- Health Canada should identify a course of action, those responsible for taking action, and timeframe.
- Health Canada should use a science-based approach to managing antimicrobial resistance.
- Health Canada should use scientifically sound risk analysis that follow the OIE guidelines and stakeholders should be consulted throughout the process of risk analysis, not just at the risk management stage.
- Health Canada should employ scientific reviews on new and existing antimicrobials used in human and animal medicine.
- Health Canada should conduct scientific reviews for new and existing growth promotion/feed efficiency products.
- The drug review process needs to become more effective, efficient, and responsive.
- Policy and regulatory decision-making must be grounded in evidence-based science.
- The impact of risk management strategy on drug availability, and continued new product research and development must be considered.
- Regulatory requirements must be transparent, predictable, and where possible, harmonized with other developed countries.
- Eliminate legislative loopholes that permit "own use" importation of antimicrobials for use in food producing animals.

III. CONSIDERATIONS

Key areas of priority that have been identified from the AMR report, stakeholders comments, international perspectives, and from an analysis of various consultation outcomes for developing Canadian strategy on antimicrobial resistance include the following:

- Risk-based analysis of new and existing antimicrobial drugs.
- Development of a sound regulatory policy on antimicrobial use and antimicrobial resistance.
- Development of an evidence-based integrated surveillance system to monitor AMR resistance and antimicrobial use in animals.
- Development of evidence-based research and educational programs to promote prudent and judicious use of antimicrobial agents and to limit the transfer of zoonotic infections from animals to humans.

On the basis of the current status of scientific knowledge on AMR and considering several international guidance documents, VDD drafted specific guidelines for assessing the microbiological safety of new veterinary antimicrobial drugs. The document was part of the NDS guidelines posted on the VDD web site for consultation. Comments have been received from drug sponsors and the final document is available on the VDD Web site. This represents a very significant outcome of the ongoing policy development process and addresses major regulatory concerns identified by the Advisory Committee.

Since some of the relevant issues that were identified in the Advisory Committee Report are currently being addressed under specific initiatives or as separate files, they are not addressed in this Issue Analysis Paper. These issues include the development of an Extra Label Drug Use Policy, development of a regulatory framework on the use of unapproved drugs, as well as initiatives on Active Pharmaceutical Ingredients (APIs).

IV. RISK ASSESSMENT AND MANAGEMENT APPROACHES

Because of the evolving nature of scientific evidence on AMR and its risk factors, proposed options have taken into consideration the need for flexibility and transparency in the decision-making process. A systematic evidence-based approach to managing the risks of AMR associated with the use of antimicrobial agents in food-producing animals is, therefore, highly recommended. This approach entails full implementation of the following four strategies:

Strategy #1: Investments in scientific risk-based analysis of new/existing antimicrobial agents that are being used in veterinary medicine and livestock production

Rationale:

This option is being proposed because it is the most transparent, yet scientifically defensible approach to risk management with respect to antimicrobial uses in animals. It should be recognized that not all antimicrobial agents are similar in the way they kill or inhibit bacteria nor in their potential to lose effectiveness due to AMR. This strategy would need to be implemented immediately in conjunction with Strategy #2.

Strategy #2: Creation of the Expert Advisory Committee on Antimicrobial Resistance Risk Assessment

Rationale:

The Expert Advisory Committee on AMR Risk Assessment will provide on-going and timely expert advice to VDD on the assessment of the risks of developing resistance to new and existing antimicrobial agents. This Committee will also provide expert advice on determination of threshold level of resistance with respect to AMR surveillance. This is clearly an emerging issue, which could become a major risk management challenge in future, especially with increasing development of resistance to antimicrobial agents that are used in both animals and humans (e.g., fluoroquinolones, cephalosporins, macrolides, streptogramins). Implementation of this strategy should proceed immediately.

Strategy #3: All veterinary antimicrobial agents that are used for disease treatment and control should be available by “prescription only” as recommended by the AMR Advisory Committee

Rationale:

On the basis of the qualitative assessment of risks and benefits of this option and with due consideration given to comments from a broad cross-section of stakeholders, this strategy will, to some extent, tighten indiscriminate use of antimicrobial agents that are also used in human medicine.

Strategy #4: Coordinate or encourage the creation of a “Stakeholder Committee on Prudent Use of Antimicrobial Agents” to be led by CVMA.

Rationale:

The intent of this initiative is to emphasize the importance of prudent use efforts and to encourage stakeholders (including veterinarians, producer groups, industry) to develop relevant

educational and research programs to promote prudent and judicious use of antimicrobial agents. This Committee should be tasked with developing tools, communications strategy, and messages aimed at promoting prudent and judicious use of antimicrobials, as well as addressing the need for developing educational programs focussing on AMR. The Canadian Committee on Antibiotic Resistance (CCAR) may have a significant role to play in coordinating this initiative. Further discussions are needed but implementation should be short-term.

Each of the strategies proposed above requires an Action Plan. At the present time, a draft Action Plan has been prepared to address the strategy dealing with re-evaluation of existing antimicrobial agents, which falls within the scope of Strategies #1 and #2.

V. PROPOSED RISK ASSESSMENT POLICY FRAMEWORK¹

1 PURPOSE

The purpose of this policy is to provide the Inter-departmental Antimicrobial Resistance (AMR) Science Committee (hereafter the Science Committee) with guidance for the conduct of AMR risk assessment of antimicrobial products (and other sources of antimicrobial resistance, including resistance genes) taking into consideration the key priorities and risk management options available under Canadian policy, legislative, and regulatory frameworks.

2 SCOPE

This policy is applicable to the conduct of AMR risk assessments of antimicrobial products (and other sources of antimicrobial resistance, including resistance genes) with potential impact on human health. The assessment will be guided by the key priorities identified by the Inter-departmental AMR Policy Committee (hereafter the Policy Committee) and the Science Committee and be in line with Health Canada's Decision-Making Framework.

3 RISK ISSUES

Specific AMR risk issues have been elaborated in the Issue Identification Paper. These include AMR associated with the use of antimicrobials in human medicine, veterinary medicine and livestock production, non-food animals, aquaculture industry, consumer products, plant agriculture, as well as those associated with environmental contamination with antimicrobial agents or antimicrobial-resistant organisms. The following priority areas have been identified (not necessarily in this order):

3.1 New and existing antimicrobials for use in terrestrial and aquatic food animal

¹This document is only an outline of the proposed policy framework for conducting risk assessment of antimicrobial resistance. Further details need to be developed.

production - consideration of various uses of antimicrobials, including therapeutic, prophylactic, and growth promotion.

- 3.2 New and existing antimicrobials for use in human medicine
- consideration of therapeutic and prophylactic uses.

4 CRITERIA FOR RISK PRIORITIZATION

- 4.1 Selection Pressure for Resistance due to Antimicrobial Use
 - 4.1.1 Antimicrobial use in human and veterinary medicine
 - 4.1.2 Agriculture
 - 4.1.3 Household use (consumer products)
- 4.2 Sources and Dissemination of Resistance (at the organism level)
 - 4.2.1 Transfer of resistance genes from antimicrobial-resistant bacteria to antimicrobial-susceptible ones
 - 4.2.2 Transfer of resistant bacteria from one individual to another, from animals to humans or humans to animals
 - 4.2.3 Spread of antimicrobial-resistant bacterial pathogens (including foodborne pathogens) to humans
- 4.3 Potential Impact on Individuals and Communities
 - 4.3.1 Impact on individuals
 - 4.3.2 Impact on communities
 - 4.3.3 Impact on employment
 - 4.3.4 Frequency and severity of health impact
 - 4.3.5 Capacity to treat and to prevent outbreak as a consequence of lack of available effective agents
 - 4.3.6 Community impacts, e.g., daycare
- 4.4 Potential Human Health Impact
 - 4.4.1 Frequency and severity
 - 4.4.2 Impact on morbidity and mortality
 - 4.4.3 Impact on hospitalization (longer stays)
 - 4.4.4 Impact on community-acquired resistant organisms
- 4.5 Potential Health Economic Impact (Health System Impact)
 - 4.5.1 Impact on health care costs (loss of least expensive drugs/accessibility to

- wide spectrum of drugs)
- 4.5.2 Capacity for diagnosis of antimicrobial-resistant infections
- 4.5.3 Capacity to prevent outbreak
- 4.5.4 Impact on hospitalization (longer stays)
- 4.6 Potential Animal Health Impact
 - 4.6.1 Impact on morbidity and mortality in animals
 - 4.6.2 Severity and duration of diseases
 - 4.6.3 Animal welfare issues
- 4.7 Potential Animal Economic Impact
 - 4.7.1 Potential trade issue
 - 4.7.2 Cost of production issue
- 4.8 International Concerns
 - 4.8.1 International policies/actions
 - 4.8.2 Impacts of global movement of people, products and animals

5 POTENTIAL RISK QUESTIONS

- 5.1 New and existing antimicrobials for use in food animal production.
 - 5.1.1 What is the probability of an adverse human health effect occurring due to an antimicrobial-resistant bacteria of animal origin, in which the resistance is attributable to the proposed use of the antimicrobial of interest?
- 5.2 New and existing antimicrobials for use in human medicine.
 - 5.2.1 What is the probability of an adverse human health effect occurring due to exposure to antimicrobial-resistant bacteria, in which the resistance is attributable to human uses of the antimicrobial of interest?

For qualitative risk assessments, the probability can be described as negligible, low, medium or high. Quantitative probability measures and estimates of uncertainty should be the output for quantitative risk assessments.

6 ROLES OF SCIENCE COMMITTEE/RISK ASSESSORS

- 6.1 To develop a risk profile² in collaboration with the Policy Committee to evaluate specific antimicrobial resistance issues in the context of public health concerns.
- 6.2 To seek guidance on risk assessment process from the Expert Advisory Committee on Antimicrobial Resistance and to enlist risk assessors from outside institutions.
- 6.3 To conduct preliminary assessment of how risk should be evaluated, in conjunction with the Expert Advisory Committee on Antimicrobial Resistance.
- 6.4 To execute preliminary qualitative assessment.
- 6.5 To advise Policy Committee on the feasibility and necessity of conducting quantitative risk assessment.
- 6.6 To examine the weight of evidence.
- 6.7 Prepare a summary of the uncertainties in the risk assessment.

7 RISK ASSESSMENT STRATEGY

- 7.1 The risk assessment process should be conducted according to the Office International des Epizooties (OIE) risk analysis methodology with a description of the hazard, release assessment, exposure assessment, consequence assessment, and risk estimation.
- 7.2 The risk assessment may be divided into three parts:
 - 7.2.1 Risk assessment of the antimicrobial drugs (chemical risk assessment);
 - 7.2.2 Risk assessment of the antimicrobial-resistant organisms (microbiological risk assessment);
 - 7.2.3 Risk assessment of the antimicrobial resistance genes (genetic risk assessment).
- 7.3 Initial qualitative assessment should address specific risk questions and explore all pathways through which the hazard could lead to adverse human health impacts.
- 7.4 A thorough assessment of the evidence for development of resistance should be conducted.
- 7.5 Sources of data may include published or unpublished scientific reports, national reports, surveillance database or any other useful information sources.
- 7.6 The assessment should include a description of the nature, sources and level of uncertainty and variability.
- 7.7 The risk analysis process should also include an assessment of the impact of intervention strategies or risk management options on risk reduction.

8 RISK MANAGEMENT OPTIONS

²A risk profile is a fundamental requirement of risk analysis, which entails an initial analysis of the risk issue from the perspectives of the nature, sources and prevalence of the hazards, the human health consequences, the distribution of risks and benefits as well as the available risk management options. The risk profile essentially puts the risk issue in a public health context. It should be developed in collaboration between the Science Committee (risk assessors) and the Policy Committee (risk managers).

- 8.1 Taking no action when none is required
- 8.2 Voluntary compliance by affected stakeholders
- 8.3 Education of affected stakeholder groups
- 8.4 Review of available prudent use guidelines to minimize resistance risks
- 8.5 Development of new guidelines (for affected stakeholders)
- 8.6 Economic incentives for affected stakeholders
- 8.7 Restriction of drug availability
- 8.8 Review of licence authorisation and/or alteration of label indications
- 8.9 License for use not granted for new antimicrobials

VI. ACTION PLAN FOR AMR RISK ANALYSIS FOR VETERINARY ANTIMICROBIALS

IDENTIFICATION OF ISSUE

As is: Health Canada recognizes the human health risks associated with the emergence of antimicrobial resistance (AMR), and is committed to containing the development and spread of AMR, and maintaining the efficacy of antimicrobials. The Health Canada's Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health has recommended the adoption of a risk-based approach for pre-approval evaluation of new antimicrobial submissions for food animals. The Committee also recommended a risk based re-evaluation of already approved antimicrobials that are important for human health and those that are approved for the claims of growth promotion. Risk-based decision-making to manage human health risks concurs with the Health Canada's evidence-based decision-making framework. Furthermore, it will complement international efforts to minimize the development of AMR in and spread from food animals. It is important to note that the EU has banned all antimicrobial growth promotants that are related to drugs used in human medicine since 1999 , and there are plans to phase out all antimicrobial growth promotants by 2006. Australia, New Zealand and the United States have also made necessary regulatory changes and have evaluated or are in the process of evaluating important veterinary antimicrobials through a risk-based analysis. VDD has recently developed Guidelines for Industry that incorporate the risk-based evaluation of antimicrobial new drug submissions. There is also a need to re-evaluate existing antimicrobials, which during their approval were not necessarily evaluated for AMR risks to human health. To assist in evaluating and managing AMR risk, Health Canada's Expert Advisory Committee on Antimicrobial Resistance Risk Assessment will provide an expert advice to this process. As other countries have already initiated this process, Canada should explore the opportunities to collaborate with other regulatory agencies and international public health organizations in managing AMR risks.

Desired state: Health Canada to approve and maintain the availability of only those antimicrobials for food animals that will not pose significant health risks to the Canadian public.

PROJECT PLAN

New veterinary antimicrobials will be evaluated as per the new guidelines which incorporates AMR risk assessment. This action plan focusses on reassessing existing antimicrobials. In general, it will involve preparing a risk profile for each antimicrobial (sequentially based on the priority list) and determining whether a full-scale risk assessment is required. If a full-scale risk assessment is considered necessary, further steps will involve efficacy data re-evaluation (for AGPs), risk assessment, public consultations and risk management decision. The detailed steps are listed below.

Steps for the AMR Risk Analysis of Existing Antimicrobials will be as follows:

- Step 1.- Prepare a draft AMR risk assessment template (working document): (completed);
- Step 2.- Search databases and prepare list of antimicrobials approved for use in food animals in Canada (completed);
- Step 3.- Prepare a draft priority list of antimicrobials for risk-based analysis (completed);
- Step 4.- Consultation with the Expert Advisory Committee regarding the priority list and the risk assessment template;
- Step 5.- Finalize the risk assessment template and the priority list of antimicrobials;
- Step 6.- Prepare a public involvement plan;
- Step 7.- Prepare a risk profile for the identified risk issue (sequentially in order of priority, and on a case-by-case basis);
- Step 8.- Presentation to the Science Issues Review Committee (SIRC) for decisions as to whether further assessment is required. The following steps (9 to 16) will be necessary only if further evaluation is required and will be done on a case-by-case basis;
- Step 9.- Inform drug sponsors of risk assessment plan and request additional data;
- Step 10.- Evaluate efficacy data for growth promotion / feed efficacy claims (CED to take the lead). If efficacy data do not support the claim, take appropriate actions;
- Step 11.- Review other risk assessments available (if any), and/or conduct a risk assessment in consultation with the Expert Advisory Committee;
- Step 12.- Present the findings to the SIRC and stakeholders, and collect feedback and input. Finalize the risk assessment;
- Step 13.- Risk management considerations: assess the impact of various options on consumers, animal health, producers, and international trade;
- Step 14.- Risk management decisions;
- Step 15.- Develop and implement public involvement plan for stakeholder consultations, education and awareness;
- Step 16.- Initiate necessary administrative / regulatory actions for implementation of management decisions;
- Step 17.- Repeat steps 6 to 15 for all prioritized risk issues (antimicrobials).

Public Involvement / Consultation Strategy:

Ensuring a reasonable certainty of no undue risk to human health is the prime objective of the human safety evaluation of veterinary drugs intended for use in food producing animals in Canada. The proposed action plan aims to re-evaluate the AMR risks to humans from antimicrobials already licenced for use in food animals in Canada which at the time of their approvals were not necessarily examined for AMR risks. Furthermore, a risk-based decision-making approach embraces management strategies that are appropriate or proportional to the expected risks from the use of a product. Health Canada is committed to making such decisions transparent. This public involvement strategy will re-emphasize our commitment to our stakeholders with respect to timely communication and consideration of issues that affect them.

Internal consultation will be done initially by face-to-face meetings and/or via teleconference in order to scope out the risk assessment draft template and the draft priority list of antimicrobials. These documents will be finalized in consultation with the Expert Advisory Committee. When required, drug sponsors will be requested for additional data on efficacy (mainly AGPs) and AMR risk assessment. Risk assessments will be conducted in consultation with the Expert Advisory Committee, and the outcome will be presented to risk managers, stakeholders, and interdepartmental Science and Policy Committees as appropriate. Management decisions will consider the outcome of risk assessment, i.e., the impact on human health, as well as other relevant factors including the impact of various options on consumers, producers, animal health and international trade. Stakeholders will be consulted at various stages in the decision-making, and on implementation of these decisions.

It is important for Canada to cooperate with other regulatory agencies and international public health organizations for information sharing on AMR risk assessment. A formal agreement with other jurisdictions may be necessary for efficient communication.

Milestones / Timelines

1. Formation of the Expert Advisory Committee on Antimicrobial Risk Assessment - Spring, 2005;
2. Preparation of the draft priority list of antimicrobials for risk based evaluation - Spring 2005;
3. Preparation of the draft risk assessment template - Spring 2005;
4. Expert Advisory Committee consultation, and finalization of the priority list and risk assessment template - Summer / Fall 2005;
5. Preparation of the public involvement plan (phase I): updates on priority list, and risk assessment template and approach (Summer/Fall 2005);
6. Initiation of the risk profile on prioritized risk issue - Fall 2005 (start).

For each drug, the following steps will be followed:

7. Preparation of risk profile for the identified risk issue;
8. SIRC considerations and decision-making (If management finds no risk, steps 9 - 15 will not be necessary for the drug);
9. Communication of the management decision to sponsors and request additional data;
10. Evaluation of efficacy data for AGP claims. If efficacy data do not support the claim, take appropriate actions;
11. Detailed risk assessment. Risk assessment models could be adopted from other regulatory agencies or available risk assessments could be reviewed as well within the Canadian context using Canadian data;
12. Preparation of public involvement plan (phase II). Internal and external (stakeholder) consultation, education and awareness;
13. Preparation of final risk assessment;
14. SIRC consideration (option analysis) and decision-making;
15. Stakeholder consultations and decision implementation;
16. Repeat Steps 6 to 14 for each antimicrobial prioritized for risk based evaluation.

Appendix 1. Proposed priority list for risk analysis of growth promotants (in descending order of importance)

Antimicrobial	Group	Human Health Significance (Category)	Animal Health significance and Other related issues	Previous Risk Assessments	
				Source and findings	Recommended actions
Virginiamycin	Streptogramin	I - Very high importance	Only category I drug, commonly used growth promoter. Also used for prophylactic/therapeutic purpose.	<p>1. Australia -Probability of resistant infection from animals low, impact of resistant infection in susceptible human - high</p> <p>2. USA:Draft risk assessment published- treatment failure in 2-39 persons per year in the US</p> <p>3. New Zealand: Drug important to human medicine, need to preserve its efficacy</p> <p>4. Industry sponsored (data for Australia and US used) - Less than 1 life saved in the US and Australia in 5 years by banning the drug</p> <p>5. EU</p>	<p>1. Australia: growth promotion claims in poultry and pigs revoked, prophylactic / therapeutic use allowed</p> <p>3. New Zealand: Growth promotion claims revoked</p> <p>5. EU: use of the drug for growth promotion banned since 1999</p>
Tylosin	Macrolide	II - High importance	Important drug in veterinary medicine. Used for treatment and prophylaxis in poultry and pigs, and prophylaxis in cattle. Used as growth promoters in pigs.	<p>1. New Zealand: All macrolides reviewed together. Drugs important to human medicine, need to preserve their efficacy</p> <p>2. Australia: Review ongoing</p> <p>3. Industry sponsored (USA) - 1 in 10 million treatment failure due to resistant campylobacter</p> <p>4. EU</p>	<p>1. New Zealand: Growth promotion claims for all macrolide revoked.</p> <p>4. EU: use of the drug for growth promotion banned since 1999</p>

Antimicrobial	Group	Human Health Significance (Category)	Animal Health significance and Other related issues	Previous Risk Assessments	
				Source and findings	Recommended actions
Erythromycin*	Macrolide	II - High importance	Mainly used in poultry for treatment and control of respiratory infections.	1. New Zealand All macrolides reviewed together (see tylosin above) 2. Australia: Review ongoing 3. EU	1. New Zealand: growth promotion claims revoked 3. EU: drug not used as AGP
Lincomycin	Lincosamide	II - High importance	Important for the treatment and prevention of swine dysentery and pneumonia. Growth promoter in chicken.	1. EU	1. EU: drug not used as an AGP
Streptomycin*	Aminoglycoside	II - High importance	Used with vitamins and other antibiotics to alleviate the impact of diseases on growth.	1. EU	1. EU: drug not used as an AGP
Neomycin*	Aminoglycoside	II - High importance	Poorly absorbed from the gut and used for treatment of bacterial enteritis mainly with other antimicrobials.	1. EU	1. EU: drug not used as an AGP
Penicillin G	Penicillin	III - Medium importance	Commonly used to treat various gram positive infections (oral or parenteral) in all animal species. Also used as growth promoters in combination with chlortetracycline and or sulfonamides.	1. USA - 1989 review by the Institute of Medicine - Penicillins as growth promoters - no significant human health impact 2. EU	1. USA: allowed for growth promotion purpose 2. EU: Drug banned as AGP in 1960s or 70s.

Antimicrobial	Group	Human Health Significance (Category)	Animal Health significance and Other related issues	Previous Risk Assessments	
				Source and findings	Recommended actions
Oxytetracycline	Tetracycline	III - Medium importance	Used parenterally to treat a range of infections including bacteria, mycoplasma, and some protozoa. Used orally for growth promotion.	1. USA- 1989 review by the Institute of Medicine - tetracycline as growth promoters - no significant human health impact 2. EU	1. USA: allowed for growth promotion purpose 2. EU: Drug banned as AGP in 1960s or 70s.
Chlortetracycline	Tetracycline	III - Medium importance	Used orally for growth promotion or disease prevention / treatment.		
Sulfamethazine	Sulfonamide	III - Medium importance	Used for treatment of various bacterial and protozoal infections in many species of animals. Other sulfas are also used parenterally.	1. EU	1. EU: Drug not used as an AGP
Bacitracin	Polypeptide	IV - Low importance	Used for treatment (topical) and growth promotion	1. New Zealand 2. EU	1. New Zealand: growth promotion claims revoked 2. EU: use of the drug for growth promotion banned since 1999
Lasalocid, Salinomycin, Monensin, Narasin	Ionophores	IV - Low importance	Commonly used group of growth promoters	1. EU	1. EU: use of the drug for growth promotion to be banned from 2006
Bambermycin	Flavophospholipols (glycolipid)	IV - Low importance	Used only for growth promotion claims	1. EU	1. EU: use of the drug for growth promotion to be banned from 2006

*The label claims for these drugs include stimulating appetite or stimulating growth rate or maintaining growth in the presence of some diseases. However, they are used for a short duration and mainly to alleviate the effects of disease. If labels are modified, they could fit as drugs with therapeutic / prophylactic claims.

Appendix 2: Proposed priority list for risk analysis of important antimicrobials used for therapeutic / prophylactic claims (in descending order of importance)

(Note: This is not a complete list of all approved antimicrobials)

Antimicrobial	Group	Human health significance (Category)	Veterinary use pattern and animal health significance	Previous risk Assessments	
				Source and findings	Recommended actions
Virginiamycin	Streptogramin	I - Very high importance	used for long-term (growth promotion and long term prophylaxis), also used for treatment	See appendix 1 - several risk assessments	
Ceftiofur	Cephalo-sporins (3 rd gen)	I - Very high importance	Drug of category I	1. UK risk assessment completed for imported cattle with resistant Salmonella Newport, not published 2. EU seeking actions on the drug	
Enrofloxacin	Fluoroquinolones	I - Very high importance	Recently approved, and has been evaluated for AMR risks	1. FDA-CVM: Therapeutic use in poultry has human health impacts 2. New Zealand: 3. UK ongoing 4. Industry sponsored (USA): No risk to human health either from the use of the drug in chicken, or cattle 5. EU seeking actions	1. Recommended to revoke the use licence in poultry 2. New Zealand: Only individual treatment of sick animals permitted, mass medication even for treatment not allowed
Tylosin, Tilmicosin, Erythromycin	Macrolide	II - High importance	Long-term use (growth promotion and long term prophylaxis). Important drug in veterinary medicine. Used for treatment and prophylaxis in poultry, treatment and prophylaxis in pigs, and prophylaxis in cattle.	1. Australia: Review ongoing 2. New Zealand: Drug considered important for human medicine 3. Tulathromycin RA from Pfizer - no risk through injectable product	2. New Zealand: No growth promotion use allowed, therapeutic / prophylactic use under veterinary supervision allowed

Antimicrobial	Group	Human health significance (Category)	Veterinary use pattern and animal health significance	Previous risk Assessments	
				Source and findings	Recommended actions
Lincomycin	Lincosamides	II - High importance	Long term use (growth promotion and long term prophylaxis).		
Ampicillin-sulbactam	Penicillin	II - High importance	Extended spectrum penicillins used for treatment of respiratory infections in cattle		
Streptomycin	Aminoglycosides	II - High importance	Long term use (growth promotion). Used for treatment of leptospirosis and GI disorders.		
Neomycin	Aminoglycosides	II - High importance	Long term use (growth promotion). Used for topical use and treatment of GI infections.		
Gentamicin	Aminoglycosides	II - High importance	Principally used topically		
Pirlimycin	Lincosamides	II - High importance	Only for intramammary use		
Tiamulin	Pleuromutilin	III - Medium importance	Long-term use (prophylaxis). Related to macrolides		
Spectinomycin	Aminocyclitol	III - Medium importance	Long-term use (prophylaxis). Related to aminoglycosides.		
Apramycin	Aminocyclitol	III - Medium importance	Related to aminoglycosides.		
Penicillin G	Penicillin	III - Medium importance	Long-term use (growth promotion and long term prophylaxis). Used in different species to treat different infections.		
Oxytetracycline	Tetracycline	III - Medium importance	Long-term use (growth promotion and long term prophylaxis). Used in different species to treat different infections.		

Antimicrobial	Group	Human health significance (Category)	Veterinary use pattern and animal health significance	Previous risk Assessments	
				Source and findings	Recommended actions
Chlortetracycline	Tetracycline	III - Medium importance	Long-term use (growth promotion and long term prophylaxis). Mainly used orally.		
Sulfamethazine	Sulphonamide	III - Medium importance	Long-term use (growth promotion and long term prophylaxis).		

**VII. GUIDANCE DOCUMENT FOR MICROBIOLOGICAL SAFETY STUDIES
REQUIREMENTS FOR PREPARATION OF VETERINARY NEW DRUG
SUBMISSIONS**

**VETERINARY DRUGS DIRECTORATE
GUIDANCE FOR INDUSTRY**

2005

Table of Contents..

2	Microbiological Safety Studies	
2.1	Veterinary Antimicrobial Products	
2.1.1	Information About the Antimicrobial	
2.1.2	Activity Spectrum of the Antimicrobial	
2.1.3	Administration of the Antimicrobial	
2.1.4	Antimicrobial Resistance Studies	
2.1.4.1	Resistance mechanism	
2.1.4.2	Transfer of antimicrobial resistance genes	
2.1.4.3	Cross-resistance	
2.1.4.4	Co-resistance	
2.1.4.5	Resistance Development	
2.1.5	Effect on the Animal Gut Microflora	
2.1.6	Effect on Human Gut Microflora	
2.1.7	Impact on Human Medicine	
2.1.8	Pharmacokinetics	
2.1.9	Historical Information	
2.1.10	Combination Antimicrobial Products	
2.1.11	Post-approval Monitoring	
2.1.12	Global Harmonization	
2.2	Direct-Fed Microbial and Competitive Exclusion Products	
2.2.1	Information About the Product	
2.2.2	Antimicrobial Resistance Profile	
2.2.3	Effect on Animal and Human Gut Microflora	

2 Microbiological Safety Studies

In this section of the Human Safety Requirements, information is provided regarding the data requirements for demonstrating the microbiological safety of a drug product. This section pertains to antimicrobial drug products as well as products containing bacteria, for example, direct-fed microbial products. For specific drug products which do not fall within these two categories, the sponsor may wish to contact the Directorate for specific human safety requirements.

2.1 Veterinary Antimicrobial Products

This section pertains to antimicrobial drug products (including antibacterials, antiparasitics and antivirals). However, information in this guidance is often targeted to antibacterial products. Sponsors submitting applications for other antimicrobial products may wish to consult with the Directorate for the specific requirements for their submission.

The impact of the use of antimicrobial products in food-producing animals on the development and the potential for enrichment and dissemination of antimicrobial resistant human bacterial pathogens is considered one of the principal aspects of the human safety review.

The objective of this guidance is to provide information necessary for assessing the potential impact of the use of veterinary antimicrobial products on the development of antimicrobial resistance in bacteria of animal origin, which may affect antimicrobial therapy in veterinary and human medicine. One of the recommendations of the *Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health*³ is to conduct risk-based evaluation of the potential human health effects of all uses of antimicrobials in food-producing animals. This guidance document emphasizes a preliminary risk analysis approach and outlines the data requirements to evaluate the potential for the development of bacterial resistance or cross-resistance to veterinary antimicrobial products as it might occur in the intended species, under the proposed conditions of use of the product as well as the potential for transfer of resistant bacteria or resistance determinants to humans.

Sectional Reports

In general, the microbiological safety studies required for assessing human safety of a veterinary antimicrobial product should include the following sectional reports. However, specific requirements may vary on the basis of importance of the proposed antimicrobial to human medicine or on its formulation usage. It is understood that some of the studies described in this section may be the same as those provided for the evaluation of target species safety and efficacy.

³ Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health. 2002. Uses of antimicrobials in food animals in Canada: Impact on resistance and human health. Available at http://www.hc-sc.gc.ca/dhp-mps/pubs/vet/amr-ram_final_report-rapport_06-27_cp-pc_e.html

If this is the case, cross reference should be provided to those studies.

2.1.1 Information about the antimicrobial

The following information should be included in this section:

- The drug's generic name, chemical name and chemical structure;
- Manufacturer's name, contact information and Canadian distributor;
- Class of antimicrobial;
- Information on the mechanism(s) of action (literature reports and/or specific studies undertaken by the sponsor);
- Characterization of the product (i.e., bacteriostatic vs. bactericidal).

2.1.2 Activity spectrum of the antimicrobial

Antimicrobial susceptibility testing should be performed according to standardized methods using appropriate quality control, and be reported quantitatively to allow comparison of results. Data from minimum inhibitory concentration (MIC) tests against a wide variety of microorganisms, or from literature reports, should be provided in order to determine the overall spectrum of activity.

- Data should be presented to show MICs for food-borne pathogens and commensal bacteria. This information can be based on literature data or on studies done by the sponsor. Based on consideration of the spectrum of activity, appropriate organisms may include:
 - Food-borne pathogens: *Salmonella* spp., *Campylobacter* spp. and *Escherichia coli* O157:H7;
 - Other food-borne bacteria: *E. coli* and *Enterococcus* spp.
- The strains or isolates that are used should be of normal susceptibility that are not already selected by selection pressure.
- Information on MICs for target animal pathogens (as per the claim on the label) may be obtained within the clinical efficacy section of the submission.
- Relevant bacterial species/serotypes should be isolated from the proposed intended species.

2.1.3 Administration of the antimicrobial

Information on administration of the antimicrobial product, whether to be given on an individual or herd/flock basis, the duration as well as the route used, should be provided to help ascertain the product's potential for the development of resistance in pathogenic organisms or normal bacterial flora of treated animals and the potential for spread of resistance to other animals.

2.1.4 Antimicrobial resistance studies

2.1.4.1 Resistance mechanism

Resistance to a given antimicrobial can be inherent to a bacterial species or genus (intrinsic or natural resistance) or resistance may be acquired by some strains within a species usually susceptible to the antimicrobial under consideration (acquired resistance). Information on the resistance mechanism(s) and information on the molecular genetic basis of resistance to the subject antimicrobial should be provided from literature or from studies performed by the sponsor. Information from related analogues within the same drug class may be provided in the absence of data on the drug substance.

Where applicable, details of microbial resistance patterns in relevant microorganisms which have emerged with the use of the proposed product elsewhere in the world and/or Canadian data should be supplied in this section. This would include changes that have been identified in MICs of the antimicrobial against isolates of relevant microorganisms collected from clinical cases, field trials or other uses of the antimicrobial product.

2.1.4.2 Transfer of antimicrobial resistance genes

Estimated rate of development of resistance or information on the occurrence, or absence, of transfer and rate of transfer of resistance gene(s) can be provided by literature information or from studies performed by the sponsor. Specific studies to evaluate the occurrence of genetic transfer may follow an internationally recognized protocol. The sponsor should consider including target animal pathogens, relevant food-borne pathogens, and relevant commensal organisms.

2.1.4.3 Cross-resistance

Information on cross-resistance in relevant microorganisms to the antimicrobial in question and other antimicrobials in the same class or other antimicrobial class should be provided in this section. This should include a phenotypic as well as genotypic description and this information can be derived from literature or from studies performed by the sponsor. If this information is not available, relevant scientific explanation must be supplied.

2.1.4.4 Co-resistance

If applicable, information on co-resistance of the antimicrobial in question with other antimicrobials can be provided by literature information or studies performed by the sponsor. This should include a phenotypic as well as genotypic description.

2.1.4.5 Resistance development

Where applicable, properly conducted studies to demonstrate *in vitro* or *in vivo* rate and extent of resistance development may be included under this section. The *in vivo* studies could include laboratory animal studies and/or field trials with target animals under the proposed conditions of use of the antimicrobial product. This section could also include *in vitro* mutation frequency studies.

2.1.5 Effect on the animal gut microflora

The sponsor should discuss in detail the information provided in the other sections of the submission in terms of the exposure of food-borne pathogens and commensal organisms to microbiologically active substance in the target animal after administration of the veterinary antimicrobial product under the proposed conditions of use, and the potential for resistance selection in such bacteria. Where available, details should be provided on the concentrations of microbiologically active compounds which might be expected to occur within the large intestine or the faeces of the intended species. Where such data are not available, details may be provided by metabolism studies relevant to the gastrointestinal tract. Information should be provided on the expected effects of the antimicrobial on colonic microorganism content (including anaerobes) and resistance patterns in relevant microorganisms in target animals or animal products. Bacteria of interest in this section would be the zoonotic enteropathogens such as *Salmonella* spp., *Campylobacter* spp. and commensal bacteria such as *E. coli* and enterococci. The main objective for this data is to determine the effect of the drug on the faecal shedding of pathogens and the duration of shedding. Relevant scientific arguments should be provided if this information is not available.

2.1.6 Effect on human gut microflora

Antimicrobial resistant bacteria from food animals may facilitate the development of antimicrobial resistance in human commensal bacteria which ordinarily colonize humans without causing infection. Hence, the *in vitro* and *in vivo* microbiological effects of the drug and its microbiologically active metabolites on the human gut flora will be reviewed as part of the human safety consideration. This information will be also used to calculate the microbiological Acceptable Daily Intake (mADI) and detailed guidance on the calculation of mADI is available in the VDD adopted VICH GL36 guideline⁴. The mADI, where applicable, could be used to determine the Maximum Residue Levels as described in the section on Residue Studies.

⁴ VICH GL36 (Safety: general approach): Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI. Available at http://www.hc-sc.gc.ca/dhp-mps/legislation/vet/guide-ld/vich/ich-cih_gl_36_e.html.

Representative microorganisms that are considered relevant for the human gut flora include species of *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Enterococcus*, *Eubacterium*, *Fusobacterium*, *Lactobacillus*, and *Peptococcus/Peptostreptococcus* and *E. coli* among others. It is recommended that a minimum of 10 strains should be tested for MIC determination. MIC determinations should be performed in accordance with recognized standardized tests in order to potentially determine mADI using VICH GL36².

2.1.7 Impact on human medicine

The impact of the new veterinary antimicrobial product used in food-producing animals on the effectiveness of existing antimicrobials used in human medicine will be considered as part of the review process. The importance of the subject antimicrobial in human medicine and its potential to cause resistance or cross-resistance to antimicrobials used in human medicine need to be evaluated. The criteria of significance include:

- Indication for the antimicrobial product and availability of alternative antimicrobial therapy in case of emergence of resistance to the particular antimicrobial;
- Antimicrobial activity and mode of action;
- The mechanism of resistance, the potential for resistance development, cross-resistance and/or co-resistance and the potential for transfer of resistance genes from resistant bacteria.

The sponsors are encouraged to provide a risk assessment on the proposed use of their specific veterinary antimicrobial product with respect to human health consequences. The risk assessment methodology used could be qualitative, semi-quantitative or quantitative.

2.1.8 Pharmacokinetics

Pharmacokinetic data may be obtained from other sections of the submission. Data relevant to microbiological safety should include the following:

- Serum/plasma concentrations versus time data;
- Half life in the intended species;
- Bioavailability;
- Protein binding;
- Pharmacokinetic/pharmacodynamic data with a particular view to anticipated drug substance concentrations in the intestinal tract.

2.1.9 Historical information

Historical information from literature or studies on previously approved uses of the antimicrobial product or related products should be provided if applicable.

2.1.10 Combination antimicrobial products

A mixture of more than two antimicrobials should be considered when no other feasible alternative is available. Sound scientific rationale should be provided to support combination of antimicrobials.

2.1.11 Post-approval monitoring

A post-approval monitoring program for the emergence of antimicrobial resistance should be considered by the manufacturer as an important aspect of the review process. In addition, issues of prudent use and the extra-label use *vis-à-vis* antimicrobial resistance surveillance should be given due consideration. Post-approval surveillance is indispensable and surveillance of resistance to antimicrobials belonging to classes considered important in human medicine should be closely monitored so as to be able to detect emergence of antimicrobial resistance in time to allow corrective strategies to be implemented as part of an efficient post-approval review.

2.1.12 Global harmonization

International approaches for the regulation of veterinary antimicrobial products will be taken into consideration in the review process (for example, VICH GL27⁵ and GL36, OIE guidelines⁶).

2.2 Direct-Fed Microbial and Competitive Exclusion Products

Direct-fed microbial products (also known as probiotics) contain known microorganisms with known quantities that claim certain health benefits. Competitive exclusion products are used to protect colonization of the intestinal tract by pathogenic bacteria such as *Salmonella* spp. by creating a physical barrier. These products generally contain unidentified live microorganisms that are isolated from the gastrointestinal tract of healthy animals. The use of both product types in food producing animals are subject to approval by the Human Safety Division of VDD.

Sectional Reports

The data submitted for competitive exclusion and direct-fed microbial products should include:

⁵ VICH GL27 (Antimicrobial resistance: pre-approval): Pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance. Available at http://vich.eudra.org/pdf/01_2004/gl27_st7f.pdf.

⁶ Office International des Epizooties (OIE). 2001. The OIE Scientific and Technical Review, 2001 December, Volume 20 (3). Paris, France.

2.2.1 Information about the product

The following information should be included in this section:

- The product name;
- The Manufacturer's name, contact information and Canadian distributor;
- The product composition: list the active ingredients including genus, species and strain. Include the source, growth and method of identification;
- The administration of the product: intended species, dosage, frequency, route of administration, and herd/flock or individual;
- Proposed storage conditions;
- The information on the pathogenicity of the individual organisms in the probiotic product to humans (including opportunistic nature of the organisms).

2.2.2 Antimicrobial resistance profile

Information on the antimicrobial resistance profile of microbial components should be provided. The values should be determined according to internationally accepted method(s).

- Information on resistance mechanism(s) of microbial components which show resistance to antimicrobials of importance to human medicine should be provided by literature review or investigations conducted by the sponsor.
- If the antimicrobial resistance proves to be genetically based, it should be shown whether or not the resistance factor is mobile and transferable to other bacteria in the same or other genera. The information may be provided based on literature review or investigations conducted by the sponsor.

2.2.3 Effect on animal and human gut microflora

Information on the safety and adverse effects of the microbial components of the product in animal and human gastrointestinal tract should be provided by literature review or by studies conducted by the sponsor to assess the microbiological safety of the proposed product.

VIII. PROPOSED CATEGORIZATION OF ANTIMICROBIAL DRUGS

Antimicrobial drugs are used primarily in human and veterinary medicine for the treatment, control and prevention of bacterial diseases. In addition, some of these drugs are also used for other purposes in the agri-food industry for instance, growth promotion and improving feed efficiency. It is well recognized that many of the same chemical classes of antimicrobial drugs used in animals are also used in humans. Some of these antimicrobials are the drugs of last resort

for the treatment of serious life-threatening infections in humans. If these drugs become ineffective due to the development of bacterial resistance, alternative antimicrobials may not be available to treat infections caused by resistant bacteria. Therefore, it is imperative to develop measures to mitigate the loss of effectiveness of these life-saving drugs. In the context of ensuring prudent and judicious use of antimicrobials, careful attention needs to be placed on how these drugs are used both in human and animals.

Health Canada recognizes that all available antimicrobial drugs are important. However, some drugs are considered more important than others in the treatment of bacterial infections. The rationale used to rank the antimicrobial drugs according to their relative importance in human medicine is given below. For the sake of simplicity, the drugs have been ranked according to their chemical class and have been placed in a category where majority of the drugs within the class may fall. It is understood that some of the individual drugs in a particular class may not fall in the same category as other drugs of the same class and such exceptions will be treated on a case-by-case basis.

This categorization system is a guide for the evaluation of veterinary new antimicrobial drug submissions. Sponsors are encouraged to take into consideration this categorization system when preparing their veterinary new drug submissions. As a general rule, drugs belonging to a higher category will receive more rigorous scrutiny as compared to the drug of a lower category. This categorization will be updated periodically as new relevant scientific information/evidence is obtained by the Directorate.

Rationale for categorization:

The criteria for categorization of antimicrobials is mainly based on the following factors:

- **Indication and availability of alternative antimicrobial therapy:** A drug which is used for serious life-threatening conditions will be given a higher score than a drug which is used routinely for common non-life-threatening infections. Consideration will be given as to whether there are any suitable alternative drugs available in case bacteria develop resistance to these drugs. For example, for a drug belonging to category I, there are limited and/or no alternatives available or the alternative drugs available are within the same category.
- **Activity and mode of action:** This includes a consideration of the spectrum of activity as well as the efficacy of a particular drug. A drug with a novel mode of action is given a higher score.
- **Mechanism of resistance and potential for transfer:** This factor encompasses consideration of resistance mechanism(s) by which bacteria develop resistance to a particular drug as well as the potential to develop cross- and co-resistance. For the potential for transfer of resistance, resistance mechanisms which are encoded on transmissible elements are given a higher score than the chromosomal encoded

mechanisms.

1. Category I: Very High Importance

These are antimicrobials of highest importance in human medicine and are used for the treatment of life-threatening bacterial infections. There may be no alternative antimicrobials in case of emergence of resistance to these agents. Some of these agents have unique mechanisms of action and hence should be reserved for the treatment of serious infections. New antimicrobial drugs with the spectrum of activity against serious life-threatening infections and/or unique modes of action will fall in this category. Examples include:

- 1.1 Carbapenems
- 1.2 Cephalosporins -third and fourth generation
- 1.3 Fluoroquinolones
- 1.4 Glycopeptides
- 1.5 Ketolides
- 1.6 Monobactams
- 1.7 Oxazolidinones
- 1.8 Streptogramins

2. Category II: High Importance

Antimicrobials classified as category II consist of those that can be used to treat severe infections and for which alternatives are generally available. Examples include:

- 2.1 Aminoglycosides Group 1 (amikacin, gentamicin, kanamycin, netilmicin, tobramycin)
- 2.2 Cephamycins
- 2.3 Lincosamides
- 2.4 Macrolides
- 2.5 Penicillins Group 1 (penicillins - β lactamase inhibitor combinations, carboxypenicilins, ureidopenicillins)
- 2.6 Rifamycins

3. Category III: Medium Importance

Majority of these antimicrobials are generally used for treatment of non-life-threatening yet common bacterial infections. Bacteria that are resistant to these drugs can be treated by category II or I antimicrobials. Examples include:

- 3.1 Aminoglycosides Group 2 (neomycin, streptomycin, spectinomycin)
- 3.2 Amphenicols
- 3.3 Cephalosporins -first and second generation except cephamycin

- 3.4 Penicillins Group 2 (natural penicillins, aminopenicillins, penicillinase resistant penicillins)
- 3.5 Polymyxins
- 3.6 Quinolones except fluoroquinolones
- 3.7 Sulphonamides
- 3.8 Tetracyclines
- 3.9 Trimethoprim

4. Category IV: Low Importance

Some of these antimicrobials are currently of limited use in human medicine while others such as the ionophores, are not used in human medicine. Examples in this category include:

- 4.1 Bacitracin
- 4.2 Coumarins
- 4.3 Flavophospholipols
- 4.4 Ionophores
- 4.5 Nitrofurans
- 4.6 Quinoxalines

IX. EXPERT ADVISORY COMMITTEE ON ANTIMICROBIAL RESISTANCE RISK ASSESSMENT

DRAFT TERMS OF REFERENCE

1. PURPOSE

In recognition of the scientific complexities of issues around antimicrobial resistance (AMR), Health Canada will seek expert advice from an Expert Advisory Committee on AMR Risk Assessment. The Committee will provide advice on available risk assessments, risk assessment methodology, and risk assessment applications to evaluate the health risks and benefits of specific antimicrobial agents in order to make evidence-based risk management decisions on the use of antimicrobial agents. Involvement of broader medical and scientific communities in the regulatory decision-making process is expected to enhance transparency and provide opportunity for proactive external guidance, thus greatly improving the antimicrobial drug review process. This in turn would lead to maintaining and improving the health and safety of Canadians.

2. SCOPE

The primary focus of the Expert Advisory Committee will be to review scientific information and provide expert advice relevant to the assessment of risks and benefits of human and non-human uses of antimicrobial agents. This will include critical review of antimicrobial resistance risk

assessment methods and results with respect to specific antimicrobial uses, their contribution to resistance and consequent human health implications.

3. ROLE AND MANDATE OF THE EXPERT ADVISORY COMMITTEE

The role of the Expert Advisory Committee is to provide on-going and timely expert advice and assistance to Health Canada on:

- methods to identify and prioritize issues relevant to the risk assessment of existing antimicrobial agents;
- the assessment of the risks and human health implications of emerging/spreading/persisting resistance to new and existing antimicrobial agents used in animal production or medicine;
- risk profile and/or risk assessment documents prepared by the interdepartmental AMR Science Committee;
- risk assessments provided by drug sponsors in support of antimicrobial new drug submissions or existing antimicrobial agents;
- issues arising directly from sponsor's antimicrobial drug submissions;
- determining new antimicrobial products that are unlikely to result in AMR in human pathogens for the purposes of priority reviews;
- interpretation of data arising from research, ongoing surveillance of AMR and antimicrobial use monitoring;
- issues arising from post-approval monitoring of AMR;
- risk management strategies or intervention measures to reduce the risks of AMR and related matters; and
- evaluation of the implementation of the recommendations of the "*Advisory Committee on Animal Uses of Antimicrobial Drugs and Impact on Resistance and Human Health*".

The Committee explores options and provides recommendations for resolution of the issue(s). Health Canada retains the ultimate decision-making authority and accountability in all cases.

4. REPORTING STRUCTURE

The Committee reports to the Director General, Veterinary Drugs Directorate (VDD), Health

Products and Food Branch, Health Canada, the lead on AMR for the Government of Canada.

5. MEMBERSHIP / PARTICIPATION / QUALIFICATIONS

The Committee consists of a small group of knowledgeable, experienced and well-recognized experts in the following medical/scientific fields:

- Risk Assessment (food safety or microbial risk assessment in particular)
- Microbiology (specifically bacteriology or specialization in antimicrobial resistance)
- Pharmacology
- Veterinary Medicine
- Human Medicine/Public Health
- Epidemiology
- Statistics

Members may also include medical/scientific professionals who could contribute to the specifics of risk assessments on AMR.

Members of the Committee are drawn from persons nominated by stakeholder groups, such as the pharmaceutical industry, health professionals, animal health organizations and academia.

Members are selected by the Director General, VDD, who will also select the Chair. The membership of the Committee as a whole may be selected to reflect an appropriate blend of gender and regional representation.

The Committee consists of five to eight members, including one lay member. The lay member is not expected to have professional training in the area of the Committee's expertise, but should be knowledgeable of current and emerging issues relating to public health.

6. TERM

Members will be appointed for a term of three years and may be extended for an additional three year term. The Director General, VDD, will endeavour to ensure that appointments of members are scheduled to allow for continuity and systematic rotation of membership.

Members who are absent from two consecutive meetings shall forfeit membership of the Committee. An individual may withdraw from the Committee at any time upon written notification to the Director General, VDD. Membership may also be terminated at any time upon written notification from the Director General.

7. MEETINGS

It is anticipated that there will be up to three Expert Advisory Committee meetings each year. Additional meetings may be held at the discretion of the Chair, in consultation with the Director General, VDD. Meetings will normally be held in the National Capital Region but a large portion of the work may be conducted through a variety of communication means, including teleconference or video conference.

Up to four Health Canada staff with expertise in the areas of the Committee may attend the meetings of the Committee as secretariat members.

8. MANAGEMENT AND ADMINISTRATION

The Advisory Committee will be supported by the federal Interdepartmental AMR Science Committee composed of members from Health Canada, Canadian Food Inspection Agency, Fisheries and Oceans Canada, and Environment Canada.

Secretariat functions will be provided by VDD. Selected program areas of Health Canada and Public Agency of Canada (PHAC) will also be included as part of the Secretariat.

The Agenda for the Committee meetings as well as briefing materials and other documentation will be sent to members in advance of meetings.

Minutes of the meeting will be circulated to members after approval by the Chair. Minutes will be kept to the minimum detail required to effectively summarize the proceedings and to accurately reflect the decisions taken. Highlights of the meetings will be made available to stakeholders at the discretion of the Director General, VDD.

Health Canada will review the role and activities of the Committee annually to ensure that it continues to meet ongoing needs.

9. COMPENSATION, INDEMNIFICATION AND LEGAL ASSISTANCE

Members will be compensated for travel expenses according to federal government policy. Members of the Committee are expected to volunteer (i.e., do not receive honoraria). Members are covered under Treasury Board's "Volunteer Policy" and automatically receive indemnification and legal assistance.

10. SECURITY CLEARANCE

All Committee members are required to undergo a security clearance to the level of "Enhanced Reliability". Security clearance, once granted, is valid for ten years.

11. CONDUCT OF MEMBERS

Committee members are expected to conduct themselves in an appropriate manner, i.e., the use of

their positions cannot be reasonably construed to be for their private gain or that of any other person, company, or organization. Confidential or protected documents leaving Health Canada must be securely stored at all times, and must be returned to Health Canada. All members are expected to protect and maintain as confidential any trade secret or privileged information divulged during the work of the Committee. Members must not discuss this information with persons not on the Committee, or divulge information obtained from the work of the Committee, including presentations made to it, until such time as this information has been officially released for public distribution.

12. CONFLICT OF INTEREST

Before appointment, all potential Committee members are required to submit conflict of interest declarations to disclose to Health Canada any circumstance that may place or be seen to place the member in a real, apparent or potential conflict of interest. It is incumbent upon the member to update his/her disclosure should his or her personal situation change.

X. TERMS OF REFERENCE OF THE INTERDEPARTMENTAL AMR SCIENCE COMMITTEE

MANDATE

To develop health risk assessments⁷ of exposure of Canadians to agents conferring antimicrobial resistance via various potential routes; to generate and evaluate potential remedial/preventive approaches/options and prioritize these based on the degree to which they minimize the risk estimates.

ROLES AND RESPONSIBILITIES

1. It is the function of committee members to i) inform the committee of issues and developments within their respective programs relevant to scientific research, international developments in the field of antimicrobial resistance, surveillance data/activities, and other relevant information in a timely manner to enable a prompt consistent unified approach to risk assessments of resistance issues; ii) to achieve consensus on scientific knowledge relating to resistance issues;
2. To provide the results of the risk assessments and provide potential approaches to the Interdepartmental antimicrobial resistance policy committee; and support the work of that committee whose challenge is the consideration of other factors (e.g., socioeconomic, cultural, ethical) in developing risk management strategies and Canadian policies with

⁷Risk Assessment involves determining the likelihood (e.g., one in a million) that a specific adverse health effect will occur following exposure to an agent, product, disease, or other factor that impacts health (As defined in the Risk Management Framework).

regards to resistance issues;

3. To obtain resources as required to augment the Committee's capacity, for example:
 - to take full account of and assess the outputs of the "Advisory Committee on Animal Uses of Antimicrobials and Impact on resistance and Human Health"
 - to take full account of the Canadian Committee on Antibiotic Resistance (CCAR);
4. To continually develop, review and update health risk assessments with supporting rationales;
5. To provide advice in a timely manner in response to day-to-day internal and external requests on antimicrobial resistance;
6. To identify and prioritize research needs and information needs and information gaps with regards to resistance issues;
7. Each representative is responsible for providing feedback on developments to their respective organization based on the records of the decisions and other committees' documents and through the use of common briefing notes to the extent possible.

REPORTING RELATIONSHIP

The Chair of the Science Committee reports to the Branch Executive Committee (BEC) / Risk Management Committee (RMC) of Health Canada's Health products and Food Branch (HPFB) and, as necessary, Health Canada's departmental Executive Committee (DEC) / Risk Management Committee (RMC) through the File Champion or his/her delegate.

XI. TERMS OF REFERENCE OF THE INTERDEPARTMENTAL AMR POLICY COMMITTEE

MANDATE

To develop Canadian policies to address the emergence and spread of antimicrobial resistance.

ROLES AND RESPONSIBILITIES

1. It is the function of the team members to inform the team of issues and developments within their respective programs (e.g., national/international standards and / or policies; economic; legal; ethical) relevant to assessing and managing risks associated with antimicrobial resistance in a timely, consistent and unified manner;
2. Consistent with the Federal Regulatory Process Management Standards, apply Health

Canada's Decision-Making Framework including the stakeholders involvement component to ensure that the AMR Policy Committee will develop risk management options based on results of Science Team's risk assessments and other considerations including social, cultural, political, environmental and economic impacts;

3. To enlist resource people as required to augment the Committee's capacity:
 - to take full account of and assess the outputs of the "Expert Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health";
 - to take full account of the Canadian Committee on Antibiotic Resistance (CCAR);
4. To provide timely advice with regards to risk management strategies/policy in response to day-to-day internal and external requests;
5. To identify and prioritize policy research needs and science gaps with regards to antimicrobial resistance;
6. Each representative is responsible for providing feedback on developments to their respective organization.

GOALS

1. To identify areas of concerns and issues regarding human and non-human uses of antimicrobial agents within the various programmes/directorates/departments. The Committee is expected to provide advice on AMR risk management strategies/policy development;
2. To participate in the ongoing AMR policy decision-making process of the Veterinary Drugs Directorate (VDD) and provide advice to the VDD AMR Team on formulating comprehensive AMR policy framework;
3. To participate in the identification and prioritization of policy research needs and science gaps with respect to antimicrobial resistance;
4. Work closely with Health Canada's AMR Science Team and review the findings and assessments of the Science Team and those of the Canadian Committee on Antibiotic Resistance (CCAR), and the "Expert Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health" for consideration in AMR policy development;
5. Review international AMR policies for consideration in the decision-making process.

REPORTING RELATIONSHIP

The Chair of the Policy Committee reports to the Branch Executive Committee (BEC) / Risk Management Committee (RMC) of Health Canada's Health Products and Food Branch (HPFB) and, as necessary, Health Canada's Departmental Executive Committee (DEC) / Risk Management Committee (RMC) through the File Champion or his/her delegate.