

# BIO AGRI MIX

## HACCP NEWS

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## WELCOME TO THE FIRST EDITION ...

BY PAUL LAKE, PRESIDENT, BIO AGRI MIX

Welcome to the first issue of Bio Agri Mix HACCP News - a document that, rather like to microorganisms central to its subject matter, evolved rapidly as a result of a range of environmental factors.

During 2001-2002 we undertook to research and prepare a series of technical documents to provide information on antibiotic resistance in general and specific information concerning the active ingredients in our product range. This work was carried out to meet our 'HACCP' obligations and during the course of it we became aware of the extreme com-

plexity of the field, the multitude of influences and the rapid changes and developments happening in disciplines as diverse as molecular biology, medicine, microbial ecology, politics, feed technology and consumer pressure groups. As a result, we felt that in addition to an annual review of our product HACCP data sheets we should also try and provide some kind of interim insight into the field on a semi-regular basis and this newsletter is the result.

Our brief is summarized below and we hope we succeed in meeting it. If you have any comments or questions please feel free to contact us at any time



**- How we deal with the complex issues surrounding antibiotic use in agriculture will be crucial to our success as an industry. We must all play our part by adopting methods of best practice to maintain the viability of the food industry, protect the environment and also safeguard the health of animals, workers and consumers -**

**Paul Lake - President, BAM**

## INSIDE THIS ISSUE:

**Antimicrobial Resistance: Situation-Canada** 2  
We examine and comment on current policy and its possible impact on the trade in a comprehensive examination of the First Report of the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health and the response to that report by Health Canada's VDD.

**Categorization of Classes of Antimicrobials** 4  
Based on Importance to Human Health

**The EU Ban** 4  
An update on the EU antibiotic ban, the legislation and its impact on the European feed additive market

## OUR CONTENT STRATEGY

Our content strategy, is firmly fixed on the use of antibiotics in food animals as therapeutics, prophylactics and growth promoters. However, because of the complexity of the subject and the implications in the present legislative and food safety climate we have broadened this basic scope to include pure scientific research in the field (where it may have feed

industry implications) political and legislative decisions in the USA, Canada and abroad, developments in alternatives to antibiotics, and quality assurance techniques to ensure the safety of the food chain of which our industry is a part.

In this, our first issue, we have concentrated on the recent report of the *Advisory Committee on Animal Uses of Antimicrobials*

and *Impact on Resistance and Human Health* and the response to this document by Health Canada because we believe the recommendations set out in these documents have major implications for our trade.

In future editions we intend to report on the milestones in this process and examine some of the practical issues

raised at the regulatory, pre-mix and feed production, veterinary, sales and distribution, farm and meat processing levels of the food chain.

Should you require more detailed information on any of the subjects covered or the issues raised then please contact us at the address given above.

## ANTIMICROBIAL-RESISTANCE: SITUATION CANADA

### Introduction

Canada has embraced the problem of resistance to antimicrobial agents and established an infrastructure to deal with this. A significant milestone has been the report of the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health (AC). Their first report focussed on providing information relevant to reducing the potential resistance and human health and safety impacts associated with animal uses of antimicrobial agents. Concluding that action should be taken to better protect the health of Canadian citizens they made a series of recommendations for Health Canada and its partners in provincial government. Health Canada proposed responses to the report through their Veterinary Drugs Directorate (VDD) and following a consultation with stakeholders developed a policy framework to implement those recommendations. We summarise the report of the AC and the VDD responses below and assess some of the possible implications for the trade.

### The Report

The report comprises 12 Chapters. C.'s 1, 2 and 5 (entitled *Introduction, Adverse Effects of Antimicrobial Resistance from Food Animals on Human Health* and *Uses of Antimicrobial Drugs in Food Animals* respectively) are descriptive only. 38 recommendations are made in the remaining chapters and 6 of these recommendations are considered to be particularly important and are given special emphasis by the AC.

#### C 3: Control of antimicrobial resistance in the human sector (1 recommendation)

The AC described the major problems related to antimicrobial resistance that exist in the human sector and efforts worldwide to control resistance in human pathogens. The impact of these efforts was analysed and it was concluded that whilst some success has been achieved many improvements are needed. Nevertheless, it was considered that lessons learned from the human sector could be applied to the food-animal sector. Consequently the AC recommended that Health Canada “*Continue support for integrated approaches to address the issue of antimicrobial resistance in humans and animals through Health Canada and organisations such as CCAR*”. Health Canada responded by describing the infrastructure that has been established and the issues that have been identified and pledged continued support of infection prevention and control and surveillance of and research into the emergence of antimicrobial-resistant pathogens.

#### C 4: Regulation and distribution of antimicrobial drugs for use in food animals (11 recommendations of which 4 are considered to be of special importance)

An overview of the regulation, distribution and sale of antimicrobials used in food-animal production in Canada and an examination of measures in place in other countries revealed a

number of regulatory gaps and other related issues concerned with, a) safety standards, criteria and assessment methods; b) external expertise and advice; c) jurisdictional and enforcement issues; d) distribution issues. As a result 11 recommendations were made, 4 of them of special importance. 6 of these are likely to have a significant impact on our trade. Recommendation 2 suggests that Health Canada should “*ensure that regulation of antimicrobials ... Includes consideration of the human health impact of antimicrobial resistance*”. Our assessment is that the implementation of this recommendation will reduce the number of growth promoting antibiotics in use, may reduce the scope for prescribing certain therapeutic substances and will introduce restrictions concerned with prudent use and good manufacturing practices at all levels. This is reinforced by the 5th and 7 recommendations to “*Wherever possible and appropriate ... Strive to harmonize veterinary drug regulatory approaches and standards with those used in other countries, especially the U.S.*” and to “*Ensure adequate coordination of federal and provincial policies concerning antimicrobial use and resistance management, and ensure the strict enforcement of ... regulations*”. The AC report goes on to recommend some measures which they consider to be especially important. Specifically Health Canada should a) “*Evaluate, register and assign a DIN [Drug Identification Number] to all antimicrobials used in food animals ... [including] antimicrobials imported in bulk ... The intent ... is to stop the direct use of APIs [Active Pharmaceutical Ingredients] in food animals.*” b) “*Stop the importation, sale and use of antimicrobials not evaluated and registered by Health Canada ... To stop—the “own-use” loophole*” c) “*Make all antimicrobials used for disease treatment and control available by prescription only*” d) “*Develop an extra-label [off-label] use policy ... [to] include the ability to prohibit the extra-label use of specific drugs of critical importance to human health*”. In addition it was also recommended that “*The prescribing and pricing of antimicrobials should not result in any incentives to dispense antimicrobials ... The Quebec approach [should be studied as] a potential national model*”. The response from Health Canada to all of these recommendations has been supportive. Significant impact on the trade is expected as a result of their implementation. Of particular importance will be the controls on “own-use” importation, extra-label use and the need for prescriptions for both prophylactic and therapeutic uses. The adoption of the Quebec model where sales of veterinary drugs are restricted to pharmacists and veterinary surgeons and where permits are required by those manufacturing and selling medicated premixes and feeds closely mirrors EU systems where the controls have had a significant effect on the structure and conduct of the trade. Financial constraints in the form of price ceilings may also be imposed.

#### C 6: Managing antimicrobial resistance risks (4 recommendations—1 of special importance)

The AC considered the human health risks from a) residues of veterinary drugs in foods and b) resistance, the assessment of which differ. Socio-economic considerations and impacts on the trade and the pharmaceutical industry were taken in to account. It was pointed out that following the scientific assessment of risk socio-economic issues should be considered before finalising the risk management strategy but it was recognised that there are many barriers in preparing cost-benefits analyses. Following an examination of the evidence for science-based policy the AC concluded that “antimicrobial use in animals should be reserved for situations where benefits are “clear and substantial” and accordingly recommended that “*sound risk analysis methods*” in a *[transparent process]* should be used to manage the risks and that “*risk-based evaluations of the potential human health effects of all uses of antimicrobial drugs in food-producing animals ... [should be conducted]... Those antimicrobials judged to be essential for human medicine should be restricted, and their use in food animals should be justified by culture and susceptibility results*”. The AC recommended that **antimicrobials for growth promotion or feed efficiency be evaluated using “*sound risk analysis principles*” and that antimicrobial claims not fulfilling criteria of efficacy, or involving products used in human therapy or likely to impair the efficacy of a prescribed product in humans through the development of resistant strains be phased out.** Health Canada endorsed these recommendations and also commented that a process to prioritize to review all the approved antimicrobial growth promoters has already begun. The products involved are penicillin, tetracycline, tylosin, virginiamycin and bacitracin. The VDD has published a list of classes of antimicrobials categorised according to risk (see table on page 4) which gives an indication of product groups that may not survive for routine use. Should Health Canada follow the lead of the EU for example and also take seriously the concept of the “precautionary principle” (essentially that risk reduction strategies should not await scientific certainty) then it is difficult to see how any of these products could remain for growth promotion use.

### **C 7: Impacts of antimicrobial resistance on animal health (2 recommendations)**

It is important to realise that antimicrobial resistance in animal pathogens impacts on human health because it can lead to veterinary use of newer substances that are often important in human medicine (e.g. the fluoroquinolone group of compounds). The main bacteria of concern in this respect are specific animal pathogens, zoonotic pathogens and commensal bacteria. The AC surveyed the evidence of resistance in these groups of organisms and concluded that it since it varies widely and Canada lacks a coordinated system of monitoring its true impact on animal health is not known. Consequently it was suggested that Health Canada “*Develop a coordinated, ongoing national surveillance system*” and “*Ensure ... dissemination of ... resistance surveillance data to ... veterinary practitioners and governments ... in a form that supports prudent use of antimicrobials in food animals*”. Health Canada sup-

ports these recommendations.

### **C 8: Strategies to ensure prudent use of antimicrobial drug: (3 recommendations)**

In 1999 the Canadian Veterinary Medical Association (CVMA) published 19 prudent-use principles. These were reviewed by the AC and generally endorsed. In addition recommendations in place in the USA and issued by other international organisations were considered. This analysis revealed gaps between the ideals of prudent use and current Canadian practice due to lack of incentives for implementation and the presence of disincentives and barriers. As a result recommendations were made concerning a) **endorsement and effective implementation of the CVMA prudent-use recommendations by veterinarians and provincial licensing bodies** and b) **antimicrobials with unique modes of action or novel resistance patterns in human medicine which should only be used in veterinary medicine in exceptional circumstances.** Health Canada broadly concurs.

### **C 9: Food safety programs used in food animal production (3 recommendations)**

Food safety programs currently in use in Canada were reviewed and whilst none currently targets antimicrobial resistance specifically they do target antimicrobial residues and are relevant to controlling resistance. The 3 recommendations suggest that “*food animal industries ... develop OFFSPs [On Farm Food Safety programs] that address antimicrobial resistance issues, subscribe to CVMA Prudent-Use-Principles, and be audited ...*” and that these activities should be encouraged by Health Canada. Again, Health Canada supported these recommendations. Implications for the trade could be onerous, particularly if extensive auditing is carried out by food commodity buyers.

### **C 10: Monitoring of antimicrobial drugs used in food animals (2 recommendations)**

There are currently no mechanisms for collecting antimicrobial use data in Canada. It was recommended that Health Canada “*Design and implement a national surveillance program ... to support risk analysis ...*” and “*Provide an annual report of antimicrobial use ...*”. Health Canada recognizes the need for monitoring and is establishing appropriate means.

### **C 11: Surveillance of antimicrobial resistance in food animals (5 recommendations; 1 of special importance)**

The AC reported that it is not possible to identify the magnitude of the resistance problem in Canada because of a lack of suitable infrastructure for monitoring. They made 5 recommendations, one of which is considered pivotal to the effect that Health Canada in consultation with the provinces should “*design and implement an ongoing, permanent, national surveillance system for antimicrobial resistance arising from food animal production ...*”. The program should be designed to support human health risk analysis using suitable indicator bacteria and it should be integrated with the surveillance of resistance in human enteric pathogens. The data obtained should be published. Health Canada’s response to

these recommendations stated that they place a high priority on the development of a national surveillance scheme and that surveillance has begun, based on schemes modelled after other international initiatives.

**C 12: Alternatives to antimicrobial drugs in food animals, research and education needs (6 recommendations)**

The AC reviewed a number of non-antimicrobial means of controlling infectious disease and concluded that additional research into these techniques to reduce the dependence on antimicrobials is necessary. It was therefore recommended that Health Canada a) “Assume a leadership role in encouraging research ... particularly on alternatives to antimicrobial ... use. Governments, producer associations, research foundations and national funding agencies should give high priority to supporting research in these areas”; b) “Support demonstration projects to evaluate programs ... to promote prudent use ... and reduce infection rates.” c) “Give priority in the regulatory assessment process for antimicrobial drugs and related products that are

*unlikely to result in ... resistance in human pathogens and to products that will reduce the use of antimicrobial drugs in animals.”* d) “Encourage [all] partners ... to improve education strategies to provide veterinarians and producers with information about ... prudent use of antimicrobial drugs and the risks of inappropriate use. Evaluate the effectiveness of educational programs on prudent use so they may continually be improved.” e) “Enhance funding to CCAR to support its ... promoting strategies aimed at preventing antimicrobial resistance. CCAR should also educate consumer groups ...” f) “Encourage Canadian veterinary colleges and veterinary associations to ensure that preventive medicine, prudent use and antimicrobial resistance are given high priority in veterinary undergraduate, postgraduate, and continuing education programs.” Health Canada supported all of these recommendations. Implications for the trade are likely to be wide and varied. Of most importance will be the opportunities to develop effective non-antibiotic feed additives to support livestock performance targets.

Category of Importance			
Category I - Very High	Category II - High	Category III - Medium	Category IV - Low
<ul style="list-style-type: none"> <li>● Fluoroquinolones</li> <li>● Glycopeptides</li> <li>● Carbapenems</li> <li>● 3rd and 4th Generation Cephalosporins</li> <li>● Streptogramins</li> <li>● Newer generation Antimicrobial Drugs</li> </ul>	<ul style="list-style-type: none"> <li>● Non-fluorinated quinolones</li> <li>● Macrolides</li> <li>● Lincosamides</li> </ul>	<ul style="list-style-type: none"> <li>● 1st and 2nd Generation Cephalosporins</li> <li>● Tetracycline</li> <li>● Aminoglycosides</li> <li>● Penicillins</li> <li>● Sulfonamides</li> <li>● Trimethoprim</li> </ul>	<ul style="list-style-type: none"> <li>● Zinc Bacitracin</li> <li>● Polymixin B</li> <li>● Colistin</li> <li>● Quinoxalines</li> <li>● Flavophospholipids</li> <li>● Ionophores</li> </ul>

**THE EU BAN ON ANTIBIOTICS**

**Summary**

During the last ten years the European Commission has become increasingly worried about the use of antibiotics in agriculture for both therapeutic (veterinary) and zootechnical (growth-promoting) purposes. Whilst there is little quantitative evidence of a contribution to antimicrobial resistance to important human and veterinary medicines as a result of agricultural use of antibiotics concern about food safety has resulted in the following situation:

- Antibiotic growth promoters (AGPs) with active ingredients used in either human or veterinary medicine have already been phased out
- Legislation prohibiting AGPs will be introduced during 2003, completing the ban. The products which will be affected

are monensin sodium, salinomycin sodium, avilamycin and flavophospholipol

- Stricter measures for coccidiostats of antibiotic origin (re-evaluation of product specific dossiers by 2006 and establishment of maximum residue levels to avoid risks to human or animal health).

**Proliferation of Unauthorised Products**

One of the important consequences of the ban on antibiotic growth promoters has been the increase in use of ‘alternative’ products. Many of these are antibacterial by nature and are derived from chemical, botanical or microbiological sources. Currently the botanical products (some of which are extremely effective) are being marketed as natural products under the EU authorisation category of ‘aromatic and appetising substances’

although growth promoting and therapeutic claims are being made. Clearly, under regulations by which additives are classified by function, some form of authorisation based on assessment of safety, quality and efficacy data is required. Many of the companies marketing such products claim that as ‘natural’ products they neither present a risk to human health nor pose any threat of antimicrobial resistance. Whilst it is true that many of them may be categorised as ‘GRAS’ claims concerning antibiotic resistance must be supported by suitable data. It is known that some commonly used chemical biocides can modify those genes that code for multiple antibiotic resistance (e.g. Triclosan; metals salts: e.g. copper).

We shall watch developments in this field with considerable interest.