



## **APVMA submission**

### **Senate Standing Committees on Finance and Public Administration Inquiry into progress in the implementation of the recommendations of the 1999 Joint Expert Technical Advisory Committee on Antibiotic Resistance**

#### **INTRODUCTION**

The APVMA contribution to the implementation of the JETACAR recommendations (as accepted in the 2000 Commonwealth Government Response) has been in two main areas. Firstly, the APVMA served on two committees established to help progress the implementation process through coordination of stakeholder activities, policy development and provision of technical advice. The APVMA served on the Commonwealth Interdepartmental JETACAR Implementation Group (CIJIG) and the Expert Advisory Group on Antimicrobial Resistance (EAGAR).

In April 2012, the APVMA accepted an invitation to serve on the Antimicrobials Resistance Standing Committee (AMRSC) established under the Australian Health Protection Principal Committee (AHPPC) of the Australian Health Ministers' Advisory Council (AHMAC).

The second area of APVMA input has been the ongoing implementation of specific recommendations under the groups of JETACAR recommendations termed Regulatory Controls and Monitoring and Surveillance.

Apart from the work done to progress the JETACAR recommendations, the APVMA has appointed a prominent expert in veterinary diagnostic microbiology and member of both JETACAR and EAGAR, Professor Mary Barton, as an APVMA science fellow.

#### **ABOUT THIS SUBMISSION**

This submission addresses the recommendations from the JETACAR report that were addressed to the then National Registration Authority (now known as the Australian Pesticides and Veterinary Medicines Authority—APVMA) as accepted by the 2000 Commonwealth Response to the JETACAR report.

#### **STEPS TAKEN BY THE APVMA**

The following outlines the actions taken by the APVMA in implementing the JETACAR recommendations accepted in the 2000 Government Response.

## **REGULATORY CONTROLS**

### **Recommendation 1**

*That Australia adopt a conservative approach to minimise the use of antibiotics in humans and animals and, to further this policy, that in-feed antibiotics used in food-producing animals for growth promotant purposes, or other routine uses where duration and dose level are the same, or very similar, should not be used unless they:*

- *are of demonstrable efficacy in livestock production under Australian farming conditions; and*
- *are rarely or never used as systemic therapeutic agents in humans or animals, or are not considered critical therapy for human use; and*
- *are not likely to impair the efficacy of any other prescribed therapeutic antibiotic or antibiotics for animal or human infections through the development of resistant strains of organisms.*

### **APVMA ACTION**

The APVMA regulatory processes acknowledge Australia's conservative approach to the registration and use of veterinary antimicrobials. To manage the risk of antimicrobial resistance posed by the veterinary use of antimicrobials, the APVMA undertakes rigorous and comprehensive risk assessment on all new antimicrobials for use in animals, major extensions of use of existing antimicrobials and reviews of currently registered antimicrobials, in accordance with Part 10 Special Data Requirements, which were updated in 2000 following the release of the JETACAR report.

The risk assessment looks at:

- *the likelihood of resistant bacteria developing in target animal from the use of veterinary antimicrobial product*
- *probability for humans to ingest bacteria in question from the relevant commodity*
- *probability that human exposure to resistant bacteria results in an adverse health consequences.*

The level of acceptable risk is that which, when weighed against proposed benefits of use in the target animal species, will not significantly compromise therapeutic use of antibiotics in humans.

Since EAGAR was disbanded in 2007, the APVMA has sought advice from the National Health and Medical Research Council (NHMRC), state and territory primary industry departments, external experts and academics.

In deciding whether or not to grant an application for registration, special attention is paid to the NHMRC's overarching concerns about the administration of antibiotics for veterinary use that are classified as 'high importance' in human medicine. For example, antibiotics from the fluoroquinolone family of antibiotics, which are classified as 'antimicrobials of high importance in human medicine', are not registered for use in food producing animals in Australia even though these antibiotics are approved for such uses in other countries with comparable regulatory regimes.

Similarly, the veterinary use of third generation cephalosporins is severely restricted. Ceftiofur is the only veterinary medicine registered from this group. Ceftiofur products are available only on veterinary prescription and must be used according to strict restraints including: no mass medication, for individual animal treatment only; not to be administered by intrammary, topical or oral route in food-producing animals; and not for use in bobby calves.

Regarding in-feed antimicrobials, the macrolides (tylosin and kitasamycin), flavophospholipol and the ionophores (monensin, lasalocid, salinomycin) are registered with growth promotion claims. This is consistent with EAGAR advice that the flavophospholipol and the ionophores are not used in human medicines and are not known to develop cross-resistance. Further information on use of macrolides is included in the discussion below on Recommendation 2.

## ***Recommendation 2***

*That the National Registration Authority (NRA) reviews the use of antibiotic growth promotants currently registered in Australia that do not appear to fulfil the criteria listed in Recommendation 1 in terms of their impact on human and animal health, using a risk analysis approach, including a cost-benefit analysis. The priority determined should be consistent with recent international reviews and use the conditions outlined in Recommendations 1 and 4.*

*It is recommended that the priority of the review at this stage be:*

- 1. glycopeptides (avoparcin is currently under review by NRA)*
- 2. streptogramins (virginiamycin)*
- 3. macrolides (tylosin, kitasamycin, oleandomycin).*

*This review is to be completed and outcomes acted upon within three years. Growth promotant claims of such antibiotics that do not pass the review process should be phased out of use within one year subject to consultation with relevant stakeholders. It is also recommended that the NRA should review the prophylactic use of avoparcin and virginiamycin in animals and the possible public health impact of this use using the parameters outlined in Recommendation 4. In order that the reviews are performed in a timely manner, it is further recommended that the federal ministers of health and agriculture ensure an adequate allocation of resources to the NRA to facilitate the rapid completion of the task and implementation of changes.*

## ***APVMA ACTION***

### ***Avoparcin***

This review was discontinued, as the registrants of avoparcin products did not renew their registrations after 30 June 2000 and the products were voluntarily withdrawn from the market.

## ***Virginiamycin***

The APVMA completed this review in 2004 and decided to cancel the registrations and label approvals of three products that were used for growth promotion and long-term prophylaxis.

The APVMA also decided to continue the registration of three remaining registered products for the prevention of necrotic enteritis in broiler chickens and to treat and prevent lactic acidosis in cattle and sheep. The APVMA varied the labels of these three products by imposing mandatory restrictions on off-label uses, which limited the duration of use of the products and the number of re-treatments that could be given in a 12-month period.

In 2005, the registrant of the three affected products applied to the Administrative Appeals Tribunal (AAT) for a review of the decision to impose mandatory restrictions. The AAT determined that the APVMA's label changes could not proceed. The registrant and the APVMA agreed on changes that would allow ongoing 'prudent use' of virginiamycin. Labels were varied to require that veterinarians must prescribe the three registered products in accordance with the Australian Veterinary Association's *Code of Practice for Prescription and Use of Products Which Contain Antimicrobial Agents*, and now bear the following mandatory prudent use statement:

- Prior to prescribing [Name of Product] investigate the use of non-antibiotic options. If virginiamycin is indicated and selected for use, prescription must be consistent with the AVA Code of Practice for Prescription and Use of Products which Contain Antimicrobial Agents. Dosage regimens should be designed for each situation with an appropriate duration and frequency to minimise treatment failure while minimising the emergence of antimicrobial resistance. Review farm records on the use of product containing virginiamycin to ensure compliance with prescribing instructions. NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL.

## ***Macrolides***

In December 2001 the APVMA began a review of selected macrolide (tylosin, kitasamycin and oleandomycin) antibiotics because of concerns over the potential risk to human health. The purpose of the review is to provide the APVMA with information to enable it to determine whether the existing uses of these macrolide antibiotics should continue in Australia. The review is in progress, pending further consideration of new developments.

### ***Recommendation 3***

*That an appropriate government authority or authorities license, or otherwise control, all importers of antibiotics (for any purpose other than individual human patient use). Licensed importers must provide import returns and distribution, and information based on amounts of active ingredient of agents intended for animal use, to the National Registration Authority, and to the Therapeutic Goods Administration for agents intended for human use.*

*It is also recommended that a much stronger audit trail for antibiotics from the importer to the end-user be implemented, particularly in the veterinary field, and that the aggregated information on import quantities are made available for scrutiny by relevant authorities and the results are made public.*

## **APVMA ACTION**

Australia has no mandatory mechanism or legal framework to collect detailed information on the use of antibiotics in animals. However, the APVMA has instituted a program which collects information from registrants of antimicrobials on the quantity of antimicrobials sold by volume. It is reasonable to assume that there is a close relationship between the quantities of antimicrobials sold and amounts used in animals. Although submission of data to APVMA is voluntary, compliance with the request has been high. In 2003, the APVMA published its first report<sup>1</sup> on the quantity of antibacterial products sold for veterinary use in Australia, for the period July 1999 to July 2002.

Due to resource constraints there was a hiatus in the collection and the publication of the report. The next report, to be published this year, will cover the period July 2005 to June 2010.

Recommendations 3 and 11 are related: see additional response at Recommendation 11.

### ***Recommendation 4***

*That the National Registration Authority (NRA) evaluate all new applications, major extensions of use and any reviews of currently registered antibiotics for use in animals by applying the recently redrafted Special Data Requirements (Part 10 of the Vet Requirements Series: Guidelines for Registering Veterinary Chemicals, NRA 1998), which includes a risk analysis of microbial resistance safety.*

## **APVMA ACTION**

Since the JETACAR report, the provision of data that address antibiotic resistance has been a mandatory APVMA requirement (Part 10 Special Data Requirement) for all new antibiotics and all major extension of uses. In 2006, the APVMA's last major revision to Part 10 included: correlation of data requirements with VICH<sup>2</sup> Guideline 27; revision to the introduction, objectives and scope; addition of references to US Food and Drug Administration and the European Medicines Agency guidelines; and provision of more details for risk assessments in non-food producing animals. Another revision is due; this may be informed by guidance documents which the World Organisation for Animal Health (the OIE) is developing.

Between 1997 and 2008, the APVMA referred submissions for at least 12 antimicrobial agents to the Working Party on Antibiotics, EAGAR and/or NHMRC for advice on antimicrobial resistance. Since the disbanding of EAGAR, the APVMA has been commissioning independent qualitative risk assessments of the Part 10 submissions before seeking advice from NHMRC.

The APVMA is obliged by its legislation to consider antimicrobial resistance on an individual product basis, in contrast to the NHMRC preference of providing technical advice to the APVMA based on classes of antibiotics.

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<sup>1</sup> [http://www.apvma.gov.au/publications/reports/docs/antimicrobials\\_1999-2002.pdf](http://www.apvma.gov.au/publications/reports/docs/antimicrobials_1999-2002.pdf)

<sup>2</sup> International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

## **MONITORING AND SURVEILLANCE**

### **Recommendation 11**

*That a comprehensive monitoring and audit system for antibiotic usage be established that covers all areas of antibiotic use. To achieve this aim, it is recommended that the federal ministers of health and agriculture form a multidisciplinary taskforce of medical, veterinary, industry and regulatory experts (including Customs, Therapeutic Goods Administration, Department of Health and Aged Care, National Registration Authority and Department of Agriculture, Fisheries and Forestry - Australia) to refine the current antibiotic import data collection and audit process, and make recommendations to relevant authorities for developing methods of monitoring and auditing usage.*

### **APVMA ACTION**

Comments on components of Recommendation 3 and 11, which are related, follow.

- a. *JETACAR recommended that an appropriate government authority or authorities should license, or otherwise control, all importers of antibiotics (for veterinary use).*
  - The legislation administered by the APVMA does not currently contain any provisions that provide for the licensing of importers of antibiotics. However, veterinary antibiotic products are categorised as ‘date controlled products’ and specific record keeping obligations for import or manufacture apply.
  - Importing of unregistered veterinary antibiotic products (or unapproved antibiotic active constituent) may constitute a breach of Section 69B of the *Agricultural and Veterinary Chemicals (Administration) Act 1992* (Administration Act). The APVMA can provide ‘consents to import’ if the intended use is veterinary. In the past 12 years, 34 import consents for antibiotic substances have been issued to veterinarians, seven to APVMA permit holders and seven to organisations conducting research under a general research permit. Twenty further applications for consents have been refused.
  - Once a veterinary antibiotic product is registered (or antibiotic constituent approved) no further authorisation to import is required by APVMA-administered legislation.
  - There are other legislative controls administered by other agencies. All importers of antibiotic products (whether for human or veterinary use and whether or not registered by the APVMA) require a Permit to Import from the Office of Chemical Safety in DoHA as all antibiotics are covered by Regulation 5A of the Customs (Prohibited Imports) Regulations 1956.

- b. *JETACAR recommended that licensed importers must provide import returns and distribution, and information based on amounts of active ingredient of agents intended for animal use, to the (APVMA), and to the Therapeutic Goods Administration for agents intended for human use.*
- Section 69E of the Administration Act establishes an obligation on people who import into, manufacture in, or export from Australia active constituents or chemical products, to submit an annual return detailing the total quantity of active constituents that were, or were included in chemical products that were imported (manufactured or exported). This provision does not apply to small quantities as prescribed in the regulations to the Administration Act.
  - In the last few years industry compliance with this provision has waned. The APVMA is investigating the development of an online reporting tool to assist industry compliance.
- c. *JETACAR recommended that a much stronger audit trail for antibiotics from the importer to the end user be implemented, particularly in the veterinary field, and that the aggregated information on import quantities are made available for scrutiny by relevant authorities and the results are made public.*
- The legislation administered by the APVMA does not contain any provisions that would provide for a system to track antibiotic products from importer to end user.
  - The APVMA permit system enables additional controls to be established and enforced. In 2012, the APVMA successfully prosecuted for non-compliance with permit conditions relevant to supply and use of the antibiotic rifampicin, which is widely considered to be an antibiotic of last resort.