NZFSA Response to

Antimicrobial Resistance Expert Panel Report

and Steering Committee Advice

August 2006

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1 Introduction

This document addresses the recommendations from the report of the Antimicrobial Resistance Expert Panel, 30 August 2005. The advice of the Antimicrobial Resistance Steering Group on the same recommendations has been included and both have informed the NZFSA responses.

For the most part NZFSA agrees with the recommendations of the Expert Panel and the Steering Group. However, the recommendations on individual active ingredients are inconsistent with the risk management policy of the Agricultural Compounds and Veterinary Medicines Group. The policy is to consider the risks posed by each trade name product unless the risks do not vary from one product to another. The Group does not consider that the risks are the same no matter what the intended purpose and circumstances. While NZFSA agrees with the intent of the recommendations, it reserves its obligation and authority to consider the risk management options on a product by product basis.

NZFSA has made clear its intended action and estimated timeframe in its responses. These are being incorporated into current work plans with sufficient priority to meet indicated deadlines.

2 Response by Recommendation

2.1 Use of Antimicrobials

1. *The development of animal disease management and good husbandry practices that minimise the routine prophylactic use of antimicrobials should be actively promoted by NZFSA, NZVA, animal industry organisations and the pharmaceutical industry.*

Steering Group response

The Steering Group noted that disease management and good husbandry practices were already actively promoted by industry organisations and the pharmaceutical industry.

NZFSA response

NZFSA agrees with the recommendation of the Expert Panel and actively assists and encourages the industry organisations and the pharmaceutical industry to examine current practices and develop strategies to minimise the use of antimicrobial products.

NZFSA also notes that the collective veterinary pharmaceutical industry has introduced a code of practice for advertising veterinary products and is establishing a forum in which best practice can be fostered.

2. *The use of streptomycin in the pip fruit and summer fruit industries should continue to be permitted under present controls.*

Steering Group response

The Steering Group supported this recommendation without further comment.

NZFSA response

NZFSA noted that, at this time, there is no satisfactory alternative for streptomycin for the treatment of fireblight in pip fruit. However, the use seems to be declining as industry's pest management initiatives take effect. NZFSA does not intend, at this time, to alter the approval for use of streptomycin for this purpose.

3. *The use of streptomycin for the treatment of tomato seedlings should be phased out.*

4. *The horticultural industries should be encouraged to continue to seek alternative strategies to control bacterial diseases so that the use of streptomycin can be phased out in the future.*

5. *Ongoing monitoring of resistance in the plant pathogens that are targets for streptomycin treatment should be undertaken*

Steering Group response

The Steering Group supported recommendations 3-5 and also recommended that NZFSA consult with industry by the end of 2006 to ascertain what steps have been taken or could be taken to give effect to the recommendations.

NZFSA response

NZFSA notes that the pip fruit and summer fruit industries are actively developing management strategies, such as integrated pest management, that are designed to reduce chemical intervention to what is necessary to manage specific pest challenges. This has led to a steady reduction in the use of streptomycin. It is expected that this trend will continue with progressively less dependence on streptomycin in the near future. Nevertheless, NZFSA will reassess the relevant plant compound products before the end of 2006. It will review the approved uses with the intention of removing the use of streptomycin on tomatoes if it is practical at this time.

As for surveillance for resistance, this is a complex issue requiring careful planning to produce useful information. NZFSA will discuss resistance surveillance with the horticulture industry in the context of developing prudent use strategies.

2.2 Regulation and Management of the Use of Antimicrobials

6. *The ACVM Act amendment to give statutory authority for applying conditions of registration to antimicrobial veterinary medicines in furtherance of public health objectives should be passed as soon as possible.*

7. *The ACVM Group should continue its present policy of classification of antimicrobial veterinary medicines for the purpose of registration (Stratification of Class I Prescription Animal Remedies, 2001), notwithstanding the potential non-compliance of the policy with the OIE Guideline (as presently drafted).*

Steering Group response

The Steering Group supported recommendations 6-7 without further comment.

NZFSA response

The Bill to amend the ACVM Act has been drafted and approved by Cabinet. It includes provision for management of risks to human health so that issues such as antibacterial resistance developing from use of antibiotics in animals or on plants can be addressed with more certainty. It is hoped that the Bill will be introduced to the House of Representatives soon so that the changes in the Act can be promulgated before the end of 2006. In the interim, NZFSA will continue, with the support of the livestock and pharmaceutical industries and the public, to impose appropriate conditions to manage the risks of antibacterial resistance.

NZFSA intends to maintain its stratification of antibiotic products with minor adjustments as a result of the Expert Panel report. It recognises that its position is not entirely consistent with OIE guidelines, but it is confident of the technical soundness of its position.

NZFSA is taking an active part in the establishment of a Codex ad hoc intergovernmental task force on resistance in bacteria to antimicrobial agents, with respect to food safety and international trade in food. NZFSA considers it essential to encourage an international perspective that minimises the risks to humans from resistance, but does not jeopardise animal health and welfare or hinder international trade in food.

8. *A programme of surveillance and monitoring of antimicrobial resistance of animal bacteria as described in Chapter 7 should be implemented as soon as practical.*

Steering Group response

The Steering Group strongly supports a programme of surveillance and monitoring, but feels that the programme outlined in the report is not detailed enough or entirely clear in its intention. It was explained that the programme was designed based on what testing was already undertaken and was a broad concept. It was not intended to be an all-encompassing programme.

The Steering Group noted this and recommended that a combined working group be established to clearly define the purpose of such a programme, to clarify the desired

outcome, to estimate its sustainability (e.g. availability of samples to allow accurate representation of the situation) and the funding implications.

NZFSA response

NZFSA considers that the development of an appropriate and robust surveillance and monitoring programme is the most problematic area of its antimicrobial resistance management strategy. It agrees with the concerns expressed by the Steering Group and supports the establishment of a combined working party to specifically address the design of such a programme.

NZFSA wants to ensure that, whatever surveillance and monitoring programme is established, it:

is appropriate for New Zealand's information needs;

provides information that can be collected and analysed over an extended period of time to identify trends and changes; and

is affordable and sustainable.

To ensure these outcomes it has commissioned a review of existing antimicrobial resistance programmes overseas to formulate its view of what is needed and what can practically be done, given New Zealand's circumstances. When the review has been considered, NZFSA will call for expressions of interest to be part of a combined working party to design a surveillance and monitoring programme. It is expected that the working party will begin its work before the end of 2006. However, depending on the advice of the working party, the programme may not be operational until 2008/09.

9. *The annual summary of statistics on sales of antimicrobial veterinary medicines should be accompanied by an analysis that shows how the medicines are used. Information on use should be obtained from industry sources and veterinarians who service the various industries. Consideration should be given to commissioning selected veterinarians to undertake periodic sentinel quantitative surveys of use within species/industries.*

Steering Group response

The Steering Group supported recommendation 9 without further comment.

NZFSA response

NZFSA will continue to collect annual sales statistics for antibiotic products. As in the past, it will include advice from relevant industry sectors. However, NZFSA agrees that more qualitative and quantitative description is needed to put sales and use information into better perspective. It accepts that the collection of contributions from industry on actual use should be formalised, maximising the practical value of such information.

How such information could be generated and reported may be unique for each sector. Therefore, NZFSA intends to carry out discussions with each sector to establish how the sector would be able to add value to the annual report. This work should be completed by the end of 2006. It is expected that novel systems (such as sentinel farms or vet practices, if appropriate) to monitor use may need to be designed and implemented, and useful data may not be available for 12 to 18 months after the systems are operational.

10. *The ACVM Group and MoH should commission the development and documentation of generic risk analyses of pathways by which humans are exposed to resistant zoonotic bacteria, and human pathogens may acquire resistance determinants of animal origin as a basis for future decisions on the registration and classification of antimicrobial veterinary medicines.*

Steering Group response

The Steering Group supported recommendation 10. However, it noted that the Expert Panel report did not provide any discussion of the issue.

NZFSA response

NZFSA also supports recommendation 10, and considers that it is essential information for a comprehensive understanding of the risks. It will discuss the matter with the Ministry of Health in the context of the MoU and the relevant operational agreement. However, NZFSA notes that investigating other than food pathways will require cooperation between separate government departments and the health sector because much of the work will be outside the normal scope of NZFSA's activities.

11. *The development and documentation of 'best practice' guidelines for veterinarians in the prudent use of antimicrobials drawing on the expertise within NZFSA, NZVA and*

its membership, the pharmaceutical industry and elsewhere should be given high priority.

Steering Group response

The Steering Group considered this to be a key recommendation. It was agreed that as the development of guidelines would provide veterinarians with a clear indication of the 'best practice' treatment options and drug hierarchy available to them, this in itself would contribute to preserving the efficacy of antimicrobial products and reduce the need for regulatory intervention. The Steering Group recommended that discussions commence as soon as practicable between NZFSA, NZVA and associated industry groups to develop these guidelines.

NZFSA response

NZFSA also agrees that this is a crucial recommendation because antimicrobial products have to be registered in a way that provides therapeutic flexibility in the face of the broad range of diseases and host species that have to be dealt with in animal health. However, NZFSA recognises that the complexity and inherent need for therapeutic flexibility makes it difficult to codify practical guidance.

NZFSA is aware of NZVA initiatives to develop appropriate best practice guidance for antimicrobial use. It is fully supportive of the work, but is also aware that it will not be an easy task to formulate simple rules for such a complex issue. NZFSA will, when appropriate, augment the guidance with modifications in conditions of registration.

The issues are complex and NZFSA does not consider it should take the lead. It considers that the primary drive to develop guidance should come from the veterinary profession, veterinary medicine specialists and the livestock and pharmaceutical industries. Nevertheless, it will encourage parties to set priorities to progress guidance where this is practical and will assist wherever it can.

12. *The proposed classification of antimicrobials used in New Zealand set out in Table 5.2 should be adopted as a resource.*

Steering Group response

The Steering Group recommended that classification of antimicrobial products should always be informed by the most recent and internationally recognised classification system. For

example, an updated classification system has been developed in Australia (EAGAR) which supercedes the JETACAR classification system which is the basis of classification (table 5.2) in the Expert Panel report.

NZFSA response

NZFSA notes the concern of the Steering Group, but it is also aware of the rapidly changing knowledge base on this subject. NZFSA is satisfied that the Expert Panel used the most recent information available to it at the time. NZFSA monitors this changing knowledge base and will refer to more recent information than the Expert Panel report, which was advice that was the best at the time it was written

2.3 Recommendations on Specific Antimicrobials

2.3.1 Aminoglycosides

13. *Evidence of synergistic effect and enhanced efficacy of mixtures of ß lactam and aminoglycoside should be required at the time of their next registration.*

14. *Oral aminoglycosides, alone or in combinations, should not be used to treat non-specific enteric infections in groups of food-producing animals. If used to treat gut infections, their selection should be confirmed by bacteriology and susceptibility tests.*

Steering Group response

The Steering Group supported recommendations 13-14 without further comment.

NZFSA response

NZFSA has encouraged registrants of products that are mixtures of β lactam and aminoglycoside active ingredients to provide information to justify their formulations, including synergistic or enhanced efficacy value for the intended purpose.

Products containing streptomycin are under consideration. In the interim they have been issued limited-time registrations (12 months), until an appropriate policy on registration of this kind of mixture can be promulgated.

Bacitracin

15. *Bacitracin resistance should be monitored as part of the surveillance system to investigate any correlation of bacitracin and vancomycin resistance trends. If no correlation is seen, this surveillance could safely be stopped.*

Steering Group response

The Steering Group noted that, while bacitracin is acknowledged as a D classified antibiotic of low concern (given there is also a question as to whether it may select for cross-resistance to vancomycin), consideration should be given to inclusion in the surveillance and monitoring programme. It was agreed that the working group being formed to develop the surveillance and monitoring programme should give special consideration to the status and inclusion of bacitracin in the programme.

NZFSA response

NZFSA agrees with recommendation 15 and will include bacitracin in the terms of reference for the working group when it is formed later in 2006.

Cephalosporins

16. *Third and fourth generation cephalosporins should be registered for use in animals with a condition that they are for use only in life-threatening conditions in individual animals where culture and susceptibility testing (done prospectively or retrospectively) provides evidence of their unique clinical value.*

17 *Registration of current third and fourth generation cephalosporins for intramammary use and any new applications for registration should be reconsidered.*

Steering Group response

The Steering Group supported recommendations 16-17 but noted that registrations for cephalosporins are considered by the ACVM Group on a 3-5 year registration lifecycle. It was felt that consideration could coincide with the next review of the relevant products.

It was noted by the Steering Group that, while there is one intramammary product registered, the conditions of registration for the product are in line with recommendation 16. The product is not registered for dry-cow therapy or routine use during lactation.

NZFSA response

NZFSA agrees with the intent of recommendation 16 and, as standard practice, will review the conditions of registration at the time of re-registration. It considers that present registrations are broadly consistent with recommendation 16. However, it recognises that such products could be used for serious conditions that are not strictly life-threatening, but would cause significant pain and distress in the affected animals.

As for intramammary use cephalosporins, it confirms that there is only one relevant registered product and its conditions of registration do not include either dry-cow therapy or routine use during lactation. NZFSA considers that the current registration conditions are adequate.

18. *Conditions of the use of first and second generation cephalosporins in dry cow therapy should be that the criteria of Appendix 2 of the New Zealand Veterinary Code of Professional Conduct be applied and that they are the treatment of choice based on herd culture and susceptibility tests.*

Steering Group response

The Steering Group supported recommendation 18 without further comment.

NZFSA response

NZFSA notes the concerns of the Expert Panel and supports the use of the VCNZ Code of Professional Conduct and NZVA's code of practice for discretionary use. However, it considers that specific risk assessments should be carried out for these active ingredients before conditions of registration are altered to limit use.

2.3.4 Fluoroquinolones

19. *The first two conditions applied to marbofloxacin boluses should be applied to all use of fluoroquinolones in food animals.*

Steering Group response

The Steering Group noted that the conditions referred to in the recommendations are:

Indiscriminate use of the product could contribute the development of antibiotic resistance. The product should be used only in individual cases of serious infections that are not likely to respond to any other antibiotic; and

The product must not be used to treat groups of food-producing animals unless bacteriology has confirmed the diagnosis and sensitivity tests have shown that it is the only alternative that is likely to be effective.

- The Steering Group supported recommendation 19 and noted that the development of guidelines as outlined in recommendation 11 will inform the most appropriate treatment option.

20. *The first condition should be applied to all fluoroquinolone use in non-food animals, and any registered indication for use that does not meet this criterion should be reconsidered.*

Steering Group response

The Steering Group supported recommendation 20, but noted the normal re-registration lifecycle of 3-5 years, suggesting that any existing registered product could be reconsidered in that context.

NZFSA response

NZFSA agrees with the intent of recommendations 19-20 and notes that the conditions on products containing fluoroquinolones for use in food animals are consistent with the recommendations. For products to be used on companion animals, NZFSA will consider if such restrictions are justified based on the risk assessments for the products.

2.3.5 Macrolides

21 *The use of macrolides and similar drugs in cattle should be discouraged.*

Steering Group response

The Steering Group noted the Expert Panel's concerns about macrolide antibiotics but felt that, as there are occasions when the use of macrolides would be clinically appropriate and a macrolide antibiotic would be the immediately obvious drug of choice, it was desirable to retain the option. It was further noted that the development of guidelines and a hierarchy of drug choice, combined with current label directions, would ensure prudent use.

NZFSA response

NZFSA agrees with the intent of recommendation 21, but it also agrees with the Steering Group in regard to retaining the use in cattle when it is prudently appropriate. NZFSA does not intend to alter the current conditions of registration.

22. *Macrolide resistance should be included in the surveillance system screens.*

Steering Group response

The Steering Group supported recommendation 22 without further comment.

NZFSA response

NZFSA agrees with recommendation 22 and will include macrolides in the terms of reference for the working group when it is formed later in 2006.

2.3.6 Anti-mycobacterial drugs

23. *None of these drugs should be registered for use in animals without a condition that they are for use only in life-threatening conditions where a culture and susceptibility has shown that no other drug is likely to work or where there are sound clinical grounds to believe they are the drug of choice.*

Steering Group response

The Steering Group supported recommendation 23 without further comment.

NZFSA response

NZFSA agrees with the intent of recommendation 23 and would apply the recommended conditions (if practical) if an application to register a relevant product was received.

2.3.7 Streptogramins

24. *Streptogramin resistance should be monitored as part of the surveillance system.*

Steering Group response

The Steering Group supported recommendation 24 without further comment.

NZFSA response

NZFSA agrees with recommendation 24 and will include streptogramins in the terms of reference for the working group when it is formed later in 2006.

2.4 Informing Regulatory Policy

25. *The present policy settings are prudent and conservative. Apart from recommendations about specific antimicrobial active ingredients, no further general restriction on the use of antimicrobials in animals seems justified.*

26. *Risk assessment protocols acceptable to both the ACVM Group and Medsafe should be developed hand in hand with the surveillance and monitoring programme proposed above. These protocols must reflect New Zealand practices because they differ from practices in other countries.*

Steering Group response

The Steering Group supported recommendations 25-26 without further comment.

NZFSA response

NZFSA accepts the advice given by the Expert Panel (and supported by the Steering Group) in recommendation 25. NZFSA is also committed to working with Medsafe in the area of risk

assessment. The interim mechanism for consideration of prescription medicines that will be used until a more formal joint consideration mechanism can be promulgated, has been agreed with the Ministry of Health.

2.5 A Surveillance Programme

27. *A surveillance programme, as outlined in Chapter 7, utilising existing/proposed microbiological sampling in the food animal industries and existing laboratory resources should be established forthwith.*

28. *The programme should be managed by an oversight committee made up of persons with the requisite expertise, nominated by the funding parties.*

29. *The pilot studies described in Chapter 7 should be initiated to run in parallel with the surveillance programme.*

Steering Group response

The Steering Group supported recommendations 27-29 with reference to recommendation 8.

NZFSA response

NZFSA agrees with the recommendations on a surveillance and monitoring programme as noted for recommendation 8.

2.6 Future Technical Advice

30. *The ACVM Group and Medsafe should appoint a standing advisory group comprising expertise in medical microbiology, epidemiology, veterinary pharmacology, animal nutrition and veterinary practice to advise them on any matters related to the use of antimicrobials in animals and plants that influence the evolution of antimicrobial resistance and on the design and interpretation of the surveillance programme.*

Steering Group response

The Steering Group supported the formation of an ongoing body to oversee the issues relating to the use of antimicrobial products in animals and on plants and antimicrobial

resistance and recommended that NZFSA commence discussions with relevant stakeholders with the view to establishing the body as soon as practicable.

NZFSA response

NZFSA accepts that the formation of an advisory body to oversee the issues relating to the management of antimicrobial resistance is desirable. While restructuring has resulted in delays in progressing this, NZFSA is now in a position to work with the Ministry of Health and other stakeholders to develop terms of reference for the advisory body and progress its establishment. It is expected that the body should be established before the end of 2006.

3 Conclusion

Considering the Expert Panel's report, NZFSA was satisfied that its regulatory management of antimicrobial products is broadly consistent with international best practice. It considers that, apart from the suggested changes for a few active ingredients, the conditions of registration are appropriate as they are. The ACVM Group will keep in mind the Expert Panel's specific recommendations for certain active ingredients as relevant products are appraised.

NZFSA recognises that more encouragement is needed to develop therapeutic and drug choice guidance, but considers that this should be driven by the interested parties so it is practical as well as prudent. NZFSA is committed to providing technical advice and expertise to assist those parties.

NZFSA considers that the area needing most attention is that concerned with developing a robust and sustainable surveillance and monitoring system. The broad concepts and suggestions of the Expert Panel are a starting point and NZFSA will establish a working party to develop the programme in more detail.

NZFSA will also establish an ongoing advisory body. However, until the body can be established, it has developed with Medsafe an operational mechanism that will ensure public health concerns are taken into account when antimicrobial products are assessed for registration.