Chapter 4

Regulatory controls of antimicrobials

4.1 This chapter addresses the effectiveness of the implementation of the JETACAR recommendations relating to regulatory control of antimicrobials. The chapter summarises the Government response to the JETACAR report and a 2003 progress report on the implementation of the recommendations. The evidence received by the committee regarding concerns about the implementation of regulatory controls on the use of antimicrobials is covered, including use in animals, use for growth promotion, off-label usage, and use in plant health.

4.2 Underlying the discussion and debate on regulatory controls is that resistance levels are driven up by increased usage of antimicrobials. In addition, as noted by Dr David Looke, reducing antimicrobial usage is one of the most effective ways to bring resistance rates down:

> [W]e need to somehow reduce the volume of antibiotics being used, and that occurs across the human sector as well as the animal and agriculture sectors. If you look at the one thing that has been proven to reduce the move towards worsening resistance it is reducing the amount of antibiotic pressure. So I think we need to try to do that across all areas. What we would like to see is that antibiotics are only ever used when they are really necessary.[1]

Implementation of the JETACAR recommendations

4.3 JETACAR recommendations 1–9 focussed on the management of antibiotic 'load' and exposure in human and veterinary medicine through regulatory controls over registration of antibiotics, imports and end-use regulations. JETACAR stated that it was 'important that the regulatory processes for antibiotics be identical or very similar for human and veterinary drugs and that microbial resistance safety is formally assessed as part of the evaluation of antibiotics for human as well as for animal use'.[2]

The Government response

4.4 In its response, the Government indicated that it accepted or supported six recommendations and began implementing or referring those recommendations. The response also indicated that the Government accepted the intent of three recommendations and offered qualified support, but took a different implementation path to that specified by the JETACAR recommendations, as follows:

- recommendation 3 (licencing importers) – the Government accepted the need for a stronger audit trail for importers to end users, but was not convinced that licencing was appropriate and opted for a reporting and audit scheme instead;

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1 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 15.

2 Joint Expert Advisory Committee on Antibiotic Resistance, *The use of antibiotics in food-producing animals: antibiotics-resistant bacteria in animals and humans*, 1999, pp xxv–xxvii.

- recommendation 5 (defining threshold/trigger rates of resistance for antibiotics in animals) – the Government agreed with the intent of the recommendation but opted for five yearly reporting of resistance data associated with antibiotic use in animals, rather than putting resistance prevalence information in product data; and
- recommendation 6 (all antibiotics for use in humans and animals be S4 prescription only drugs) – the Government accepted the concept of the recommendation, however, it indicated that there may be a need for exemptions where the risk is low or acceptable. The need to take into account existing industry codes of practice in implementing control of in-feed and drinking water use of antibiotics was also noted.[3]

Actions since JETACAR and current arrangements

4.5 In March 2003, the CIJIG released a progress report on the implementation of JETACAR. In relation to regulatory controls, the progress report noted that recommendations were being implemented, for example, the three reviews of growth promotants suggested under recommendation 2 had been initiated and activities were underway to improve national data on antibiotic prescribing in response to recommendation 3. In relation to recommendation 6, consideration of inclusion of antimicrobials for S4 scheduling was being undertaken.[4]

4.6 DAFF stated that APVMA had fulfilled all of its obligations in relation to the relevant regulatory control recommendations.[5] Actions included the completion of the review of virginiamycin and negotiation with the Australian Veterinary Association for a code of practice on the prudent use of antimicrobials.[6]

4.7 In relation to human medicine, DoHA set out the key regulatory mechanisms that are currently in place in Australia, which include:

- prohibition of the importation of antibiotic substances unless permission has been granted by the Department, in accordance with Regulation 5A of the Customs (Prohibited Imports) Regulations 1956;
- the scheduling of the majority of antibiotics as prescription only medicines, which places controls on their supply and use where there is a potential risk to public health and safety, including from resistant strains of microorganisms; and

3 Department of Health and Ageing and portfolio bodies joint submission, *Submission 32, Attachment 1*, The Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR), August 2000, pp 9–16.

4 Commonwealth Interdepartmental JETACAR Implementation Group, *Progress Repor*t, March 2003, pp 2–4.

5 Department of Agriculture, Fisheries and Forestry, *Submission 12*, p. 3.

6 Ms Kareena Arthy, Chief Executive Officer, Australian Pesticides and Veterinary Medicines Authority, *Committee Hansard*, 7 March 2013, p. 63.

- that any product for which therapeutic claims are made must be listed, registered or included in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia.[7]

4.8 DoHA noted the recent accreditation change for hospitals which require them to have antibiotic stewardship programs in place. The ACSQHC has undertaken work on the implementation of Standard 3 of the National Safety and Quality Health Service (NSQHS) Standards, "Preventing and Controlling Healthcare Associated Infection". The standard aims to ensure appropriate prescribing of antimicrobials by requiring the implementation of antimicrobial stewardship programs to influence prescribing and use of antimicrobials.

4.9 The Government has also utilised the Pharmaceutical Benefits Scheme (PBS) as a mechanism to ensure that the approvals for antibiotics subsidised under this scheme encourage judicious and appropriate use. In addition, general practices have been encouraged to achieve accreditation against the Royal Australian College of General Practitioners (RACGP) standards for general practices. The standards include a requirement that practices have systems in place that minimise the risk of healthcare associated infections.[8]

Industry actions

4.10 Industry groups provided information on regulatory controls in the agricultural sector. The Veterinary Manufacturers and Distributors Association noted that it had engaged with the APVMA and contributed to the management of AMR issues associated with JETACAR initiatives.[9] The Animal Health Alliance informed the committee that:

> The Alliance and its member companies have actively engaged with government and federal regulators – particularly Australian Pesticides and Veterinary Medicines Authority (APVMA) – in the regulatory activities initiated out of the JETACAR report recommendations. The Alliance has always supported risk based regulatory decisions made on the latest scientific information.[10]

4.11 The ACMF emphasised to the committee that it does not support the use of antibiotics for growth promotion in chickens. The ACMF supported the classification of all antibacterial agents as prescription only.[11]

4.12 In relation to JETACAR recommendation 3 – a stronger audit trail for antibiotics from the importer to the end-user – industry now has record keeping

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7 Department of Health and Ageing and portfolio bodies joint submission, *Submission 32*, pp 4–8.

8 Department of Health and Ageing and portfolio bodies joint submission, *Submission 32*, pp 4–8; see also Australia Society for Antimicrobials, *Submission 5*, p. 3.

9 Veterinary Manufacturers and Distributors Association, *Submission 2*, p. 1.

10 Animal Health Alliance (Australia) Ltd, *Submission 1*, p. 2.

11 Australian Chicken Meat Federation, *Submission 24*, pp 2–3.

requirements embedded within assurance programs.[12] Australian Pork Limited (APL) also outlined the measures its industry has put in place to manage antibiotics including that control of antibiotics on farms is handled through herd health programs, supported by Standard Operating Procedures and competent staff. The states and territories also regulate competency requirements for staff. Additionally, relevant herds must also have an approved medications list signed by a veterinarian that includes:

- descriptions of clinical signs of diseases and the medications to use;
- any in-feed medications used; and
- dose rate to apply and if used as label or off-label.[13]

4.13 Professor Cooper, also pointed to the success of self-regulation in relation to use of third-generation cephalosporin antibiotics in chickens. Third generation cephalosporin antibiotics are important antibiotics for human medicine, as they are very broad in their activity and very safe to use.[14] Professor Cooper stated:

> [I]ndustry should be applauded for selfregulation here; the Australian Poultry Industry decided not to use a third-generation drug called cephalosporin in chickens. As a result, the level of drug resistance in human infections is 3% in Australia, compared to more than 50% in countries that use the drugs.[15]

4.14 The ALFA also informed the committee that antibiotics have been used by livestock industries to treat sickness for over 50 years, noting that resistance issues in human health were a more recent phenomenon. ALFA also submitted to the committee that:

> The use of antibiotics in the cattle feedlot industry is extremely low with only 1-3% of cattle treated in any one year. This is because antibiotics are overwhelmingly used only after infection is detected. i.e. as per their use in human medicine. Notably, they are not used for growth promotion purposes.
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> Whilst the food safety regulator, Food Standards Australia and New Zealand has determined that microbial loads are low in the red meat supply chain, the cattle feedlot sector has introduced a number of best management practices to reduce such loads further so that cattle health is improved and the requirement for antibiotics reduced.[16]

12 Joint submission by Cattle Council of Australia and Sheepmeat Council of Australia, *Submission 16*, p. 7.

13 Australian Pork Limited, *Submission 27*, p. 4.

14 Associate Professor Thomas Gottlieb, *Committee Hansard*, 7 March 2013, p. 40.

15 Professor Matthew Cooper, *Submission 23*, p. 6.

16 Australian Lot Feeders' Association, *Submission 11*, p. 1.

Concerns about the implementation of the recommendations

4.15 In contrast to the views of DAFF and DoHA, witnesses questioned the effectiveness of regulatory arrangements to manage AMR in Australia. The concerns covered issues relating to use of antimicrobials including use in animals, use for growth promotion, off-label usage, use in plant health and non-clinical use of metal based antimicrobials. In addition, the lack of a cohesive and integrated approach was also raised in relation to regulatory controls.

Antibiotic stewardship

4.16 Overuse of antibiotics in Australia remains a challenge to manage, despite recent progress, with NPS MedicineWise stating that 'every unnecessary antibiotic prescribed contributes to resistance'.[17] Antibiotic stewardship aims to ensure that antibiotics are only prescribed when they are required.

4.17 As stated above, ACSQHC has worked to implement standard 3 of NSQHS Standards. As a consequence, all hospitals and healthcare facilities must have a stewardship program in place in order to be accredited. Professor Baggoley, commented that the NSQHS Standards are now mandated for over 1,500 hospitals and health services. Professor Baggoley concluded:

> I believe this approach gives us a very strong foundation in moving forward with our efforts for the prevention and containment of antimicrobial resistance in Australia and provides an excellent opportunity for Australia to further expand and strengthen its response to this continually evolving global health challenge.[18]

4.18 The Royal Australasian College of Physicians also supported the implementation of stewardship programs in hospitals.[19] Dr David Looke, commented that the adoption of standard 3 was a significant step forward.[20] However, the ASID also stated that 'the efficacy of this initiative in reducing antimicrobial usage and consequently resistance is as yet unknown'.[21]

4.19 Another submitter who sounded a note of caution was Associate Professor Gottlieb. He noted the development of stewardship programs but voiced concern with the effectiveness of their implementation:

> I fear that the problem is that there is a lot of lip service by administrations in hospitals regarding microbial stewardship. They see it written down on paper as a mandated thing they have to do, but they find ways of just

17 NPS MedicineWise, *Submission 30*, p. 1.

18 Professor Chris Baggoley, Chief Medical Officer, Department of Health and Ageing, *Committee Hansard*, 7 March 2013, p. 51.

19 The Royal Australasian College of Physicians, *Submission 37*, p. 2.

20 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 15.

21 Australasian Society for Infectious Diseases, *Submission 18*, p. 3.

> looking like things are being done rather than committing funds to it, because you do need to put funds into this.[22]

4.20 Concerns about the implementation of Standard 3 and the issue of incentives to encourage implementation are discussed in Chapter 6.

4.21 A further issue raised by submitters was that current stewardship programs do not address prescribing of antibiotics by general practitioners.[23] Dr Looke commented:

> One of the biggest challenges is going to be to move that out into the community and into community practice, because most people get their antibiotics prescribed by people who are private businessmen in their own practices, and these are in general practice and specialist medical centres. Of course, the types of stewardship programs that are being mandated through accreditation have really no impact on that area.[24]

4.22 Dr Looke went on to comment that the National Prescribing Service has committed to an ongoing program addressing antibiotic prescribing. For example, in 2012 it focused on prescribing for respiratory infections.[25] NPS MedicineWise also submitted that there needs to be a consistent and concerted effort to ensure practitioners better adhere to best practice guidelines for these medicines.[26]

4.23 Extension of antibiotic stewardship beyond healthcare institutions to community care, long-term care facilities and non-medical antibiotic use was recommended by the Antimicrobial Resistance Summit 2011.[27]

4.24 Prescribing practices in the community are addressed further in Chapter 5 in the discussion on education.

Antibiotics usage in animals

4.25 JETACAR noted the benefits of antibiotic use in animals, including economic benefits. However, the use of antibiotics in food-producing animals can result in resistant bacteria in food-producing animals that can then cause resistant infections in humans. It is also possible but yet to be established that antibiotic residues coming through the food supply could increase resistance when consumed.[28] JETACAR's

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22 Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials, *Committee Hansard*, 7 March 2013, p. 42.

23 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 15; Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials, *Committee Hansard*, 7 March 2013, p. 42; Australian Society for Antimicrobials, *Submission 5*, pp 6–7.

24 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 15.

25 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 15.

26 NPS MedicineWise, *Submission 30*, p. 1.

27 Australian Society for Antimicrobials, *Submission 5*, pp 6–7.

28 Joint Expert Advisory Committee on Antibiotic Resistance, *The use of antibiotics in food-producing animals: antibiotics-resistant bacteria in animals and humans*, 1999, pp xviii–xx.

recommendations included the review of the use of antibiotics as growth promotants and prohibition of off-label use of veterinary chemicals including antibiotics.

4.26 Dr Mark Shipp, DAFF, indicated that antimicrobials have a variety of uses in agriculture and noted that they are used in animals under regulatory controls to underpin animal health, animal production and animal welfare. The health and productivity of farm animals are improved by the responsible use of antimicrobial agents including antibiotics. The productivity of livestock industries in Australia is important to ensuring a plentiful, affordable and safe food supply. Antimicrobials are also essential in veterinary medicine for pets.[29]

4.27 While the importance of the use of antimicrobials for animal health, production and welfare is recognised, the impact of antibiotic use in the food chain on human health also needs to be considered. Professor Collignon stated that 'there is good evidence that these resistant bacteria that develop in food animals come through the food chain, are carried by people and then they cause serious infections in people'. He pointed to the Netherlands where currently between 25–50 per cent of the E. coli superbug (which is resistant to all third generation cephalosporins) is causing serious disease including blood stream infections in people and appears to be derived in large part from poultry sources.[30]

4.28 In relation to the control of antibiotic usage in animals, submitters pointed to the success in Australia of minimising resistance to fluoroquinolone. Use of fluoroquinolone is banned for use in food animals in Australia. Its use in human medicine is also restricted. It was noted that even though Australians use large quantities of antibiotics, Australia has one of lowest fluoroquinolone resistance rates in the world in humans as well as almost no resistance in food animals.[31]

4.29 Submitters argued that these examples pointed to the importance of the implementation of the JETACAR recommendations relating to antibiotic use in animals to minimise the development of resistant bacteria in humans. Submitters considered that further regulation of antibiotic use in animals is required. Professor Collignon, for example, commented that 'antibiotics are used in food animals in ways that are not used in humans and that most physicians and people in the community would regard as "abuse" of antibiotics and very poor practice'.[32]

4.30 Professor Cooper added his view on the need to implement stricter controls on the use of antibiotics in the food chain:

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29 Dr Mark Shipp, Australian Chief Veterinary Officer, Department of Agriculture, Fisheries and Forestry, *Committee Hansard*, 7 March 2013, p. 63.

30 Professor Peter Collignon, *Submission 34*, p. 2.

31 Public Health Association of Australia, *Submission* 14, p. 10; Australian Veterinary Association, *Submission* 35, p. 6; Dr Gregory Crocetti, Friends of the Earth, *Committee Hansard*, 7 March 2013, p. 3; Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials, *Committee Hansard*, 7 March 2013, p. 39; Professor Peter Collignon, *Committee Hansard*, 7 March 2013, p. 32.

32 Professor Peter Collignon, *Submission 34*, p. 2.

> The Australian Dept. of Health and Ageing notes that 'Australia's food supply is one of the safest and cleanest in the world'. We are lucky in Australia in that we enjoy access to a high standard of healthcare. Whilst it is inhumane to withhold antibiotics for veterinary care of sick animals, Australia needs to think carefully about our attitude to risk and antibiotic use. With superbugs appearing more often in hospitals and causing more deaths, what risks are we prepared to take with human health if we continue to use antibiotics as growth promoters in animals?[33]

4.31 Professor Grayson, also noted the need for better regulation in the agricultural sector and commented:

> I think for human use we have a pretty tight system—it can always be improved—but in agriculture it is still not tight enough; it is not defined. We have rules and we have regulations: 'You will do this or you won't do that,' but they are not policed or checked. So there needs to be a surveillance program about drug use in agriculture, as there is to some degree in humans.[34]

4.32 The following discussion addresses significant matters raised in relation to the use of antibiotics in the food chain: the use of antibiotics as growth promotants; use in intensive farming; off-label use of antibiotics; and use of 'critically important' antibiotics.

Antibiotic growth promotants

4.33 Antibiotics are used as growth promotants in food animals to destroy or inhibit bacteria. They are administered at a low, sub therapeutic dose. The use of antibiotics for growth promotion has arisen as more intensive farming methods have been developed. Infectious agents reduce the yield of farmed food animals and sub therapeutic doses of antibiotics are fed to animals to control these agents.

4.34 JETACAR noted that with advances in animal husbandry, genetics, disease control and nutrition, antibiotic growth promotants are only one means of improving productivity. JETACAR recommended that in-feed antibiotics should not be used in food producing animals for growth promotant purposes unless they meet certain requirements (recommendation 1). In addition, JETACAR recommended the review of three classes of antibiotics used as growth promotants and that those which failed the review process be phased out of use for this purpose. JETACAR also recommended (Recommendation 13) the development of alternatives to antibiotic growth promoters such as vaccination and improvements in feed formulation and hygiene.[35]

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33 Professor Matthew Cooper, *Submission 23*, p. 6.

34 Professor M Lindsay Grayson, *Committee Hansard*, 7 March 2013, p. 10.

35 Joint Expert Advisory Committee on Antibiotic Resistance, *The use of antibiotics in food-producing animals: antibiotics-resistant bacteria in animals and humans*, 1999, pp xxvii, xxvi –xxvi, xxix.

4.35 Professor Collignon was also of the view that the use of antibiotics as growth promotants is now less important for growth promotion for animals than antibiotic use for this purpose when discovered in the 1950s:

> What is interesting is that after use of these antibiotics for 50 years for that purpose in animals, if you look at the data now from big poultry producers in the US, the Danish data that the WHO reviewed and others, it shows that if you use routine antibiotics for either prevention or growth promotion in animals reared under reasonable and good conditions it does not make the animals grow faster.[36]

4.36 Professor Barton commented that no new growth promotants have been registered since JETACAR reported. However, a number of antibiotics continue to be registered and used in the food producing industry as growth promotants including some macrolides such as kitasamycin and tylosin. In addition, most antimicrobial growth promotants are now available as prescription only. However, Professor Barton went on to comment that 'the use pattern is still that of growth promotant use i.e. used for extensive periods of time or even the whole life of the animal' and that the use of macrolides will facilitate the growth in resistance.[37]

4.37 In addition there were concerns that the benefits of using antibiotics in animals had not been evaluated in the context of the risks. Professor Grayson commented:

> A lot of the intensive farming practices, whether it is chickens or pork, should be reassessed. We should ask: 'What is the risk-benefit for that? If we manage them in a slightly different way, would we need antibiotics?'
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> If you look back through human health the key things that improved our lives were not actually antibiotics; they were clean water, appropriate housing and reduction of overcrowding. I think we have forgotten those three rules when it comes to agriculture in the drive to try to produce food at a slightly cheaper price. We need to ask people now, 'Would you rather good quality food'—which most Australian food is—'and pay slightly more or would you rather slightly cheaper but at a risk-benefit ratio?' At the moment we do not know what that ratio is and I think we need to define it better.[38]

4.38 Submitters supported the cessation of the use of antibiotics for growth promotion. The Australian Veterinary Association, for example, stated:

> Sub-therapeutic use of antimicrobials is a strong driver of the emergence of antimicrobial resistant bacteria and antimicrobial growth promotant use should cease as soon as practicable.[39]

4.39 Professor Collignon noted that there has been wide-spread support for the banning of antibiotic usage as growth promotants and some governments have taken

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36 Professor Peter Collignon, *Committee Hansard*, 7 March 2013, pp 33–34.

37 Professor Mary Barton, *Submission 7*, p. 1.

38 Professor M Lindsay Grayson, *Committee Hansard*, 7 March 2013, p. 11.

39 Australian Veterinary Association, *Submission 35*, p. 14.

this action. However, some pharmaceutical companies have responded to these moves by redefining the word 'therapeutic' so that this term now also encompasses the routine use of antibiotics as prevention or prophylaxis. Professor Collignon went on to state:

> This is also often just continuing to use the same antibiotics in the same doses as they were previously used when it was called "growth promotion". I think this is an abuse of the term "therapeutic" and is designed to just mislead governments, farmers and consumers. The JETACAR report defined these terms and made it clear that if antibiotics were given in the same way as "growth promoters" that that practice is inappropriate and needs proper regulatory evaluation. Yet this "prophylactic" practice seems to continue in Australia and internationally.[40]

4.40 DAFF provided information on 'prophylactic use' and 'therapeutic use' and stated that the boundary between the two is 'not always clear'. Applications to change from use as a growth promotant 'would receive careful scrutiny to ensure that it did not infringe on the policy set out in the [JETACAR] recommendation' (recommendation 1). DAFF went on to comment that an application of this type was 'unlikely'.[41]

4.41 The Animal Health Alliance, which represents animal health product manufacturers, stated that it has worked cooperatively with APVMA to deliver improvements recommended by JETACAR including:

> That the use of antibiotic growth promotants in food-producing animals should not be used unless they:
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> - are of demonstrable efficacy in livestock production under Australian farming conditions;
> - are rarely or never used as systemic therapeutic agents in humans and 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.[42]

4.42 Industry groups also responded to concerns about the use of antibiotics for growth in food animals. The ACMF, for example, commented:

> While ACMF supports the use of evidence in decision making, in recognition and appreciation of consumer concerns, the ACMF antibiotic policy does not support the use of antibiotics for growth promotion of chickens.[43]

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40 Professor Peter Collignon, *Submission 34*, p. 2.

41 Senate Rural and Regional Affairs and Transport Legislation Committee, Budget Estimates 2012–13, *Answer to question on notice No. 272, Department of Agriculture, Fisheries and Forestry*.

42 Animal Health Alliance (Australia) Ltd, *Submission 1*, p. 2.

43 Australian Chicken Meat Federation Ltd, *Submission 24*, p. 2.

4.43 APL stated that since JETACAR reported 'no evidence has emerged showing that antibiotic effectiveness in humans has been undermined as a result of any antibiotic prescribed in the pork industry'. The APL added:

> Antibiotics are not used in the Australian pork industry for growth promotant purposes. Antibiotics are only used for either prophylactic use (to prevent a disease from occurring) or therapeutic use (to treat a disease once it has occurred). For this reason, antibiotic usage in the Australian pig herd is markedly less than many of our international trading partners, including the USA, Japan, Spain and many other industrialised nations.[44]

4.44 The APL went on to state that the aim of the industry is to minimise the use of antibiotics through vaccines and better management of animals.[45]

4.45 Professor Barton also commented on the steps taken by the pig industry:

> The pig industry has clearly taken antimicrobial resistance very seriously and the Pork CRC has a strategy to reduce antimicrobial use by 50% in 5 years. Unfortunately the other industries do not recognise a problem and so antimicrobial resistance is a low priority or seen as a public health issue that is not their responsibility.[46]

Intensive farming

4.46 In addition to growth promotion, other agricultural uses of antibiotics can also drive the development of AMR. In particular, the preventative uses in intensive farming were raised. Friends of the Earth Australia stated that sub-therapeutic doses of antibiotics are used to maintain animal health of livestock in the intensive farming sector. Friends of the Earth Australia argued for a ban on non-therapeutic use of antibiotics in agriculture.[47]

4.47 Professor Collignon also pointed to the changes in antibiotic usage in Holland, where significant improvements have been seen, without adverse effects in industry profitability:

> Holland, for instance, has done that. Antibiotics are used in people in the Netherlands at around the lowest rate in the world. It is half of what we use in defined daily doses per person. But they perversely had the highest use of antibiotics in the EU, so their vets were out of sync with human medicine. …What is interesting is that my understanding from hearing somebody from there a couple of weeks ago is that they have decreased the volumes by 70 per cent without any evidence that this has hugely disadvantaged the animal production sector in a global sense. Exactly the same happened in Denmark…There has been a decrease overall of about 50 per cent in the

44 Australian Pork Limited, *Submission 27*, p. 2.

45 Australian Pork Limited, *Submission 27*, p. 3.

46 Professor Mary Barton, *Submission 7*, p. 4.

47 Friends of the Earth Australia, *Submission 3*, pp 4–5.

> total amount of antibiotics used in that country, and they are still producing more pork; they are still one of the biggest pork exporters in the world.[48]

4.48 Some positive steps are being taken to find innovative ways to produce food without using antibiotics, including other ways of preventing infections. Dr Looke informed the committee that successful outcomes have been achieved in aquaculture and the chicken industry:

> I know from personally speaking to people that there is now a lot of commitment in agriculture to try to work out how to do food production without antibiotics. I note that there was some work done in aquaculture, with trying to do prawn farming without adding antimicrobials, and it was quite successful. There has been work in [the] chicken industry with breeding different types of chicken stock that are resistant to the common infections that spread through the high-intensity chicken breeding industries and they do need to put antibiotics in the feed and the water for those types of things.[49]

4.49 Dr Looke concluded that innovation and ways of preventing infections should be promoted. This may mean research into vaccine development or ways of preventing the common infections.[50] Alternatives to antibiotics in intensive farming are also discussed further in chapter 5.

Off-label use of antimicrobials

4.50 JETACAR recommended that off-label use of a veterinary chemical product be made an offence. 'Off-label' use is defined in the JETACAR report as 'a use practised by, or prescribed by, a registered veterinarian where the label directions…are varied. For example, use on a different species…or by varying the dose regime'.[51] The ASA noted that this recommendation was not implemented.[52]

4.51 Currently, legal limits have been placed on the 'off-label' prescribing of drugs by veterinarians under national control-of-use principles adopted by most states and territories. These limits generally include:

- a ban on the use of unregistered products, to treat food-producing animals, with the exception of single animals;
- a limitation on off-label use, prescribing or authorising for food-producing animals of drugs and other veterinary chemicals unless they are already registered in at least one major food producing species;

48 Professor Peter Collignon, *Committee Hansard, 7 March 2013*, pp 34–35.

49 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 15.

50 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 15.

51 Joint Expert Advisory Committee on Antibiotic Resistance, *The use of antibiotics in food-producing animals: antibiotics-resistant bacteria in animals and humans*, 1999, p. 221.

52 Australia Society for Antimicrobials, *Submission 5*, p. 4.

- a ban on use (or prescription/authorisation) contrary to any instructions under a 'Restraint(s)' heading on a product label;
- a requirement to ensure all treated animals are adequately identified, sufficient to last until the expiry of any relevant withholding period; and
- a ban on formulating, dispensing or using a veterinary chemical, registered for oral or external use, as an injection.[53]

4.52 DAFF noted that there is no general APVMA risk assessment covering off-label use of antibiotics in veterinary practice, as it is seldom possible to foresee all off-label uses. The APVMA may decide, following its risk assessment for an individual antibiotic product or a specific active constituent, to impose conditions of use that may include controls on off-label use. Conditions of use specified on a product label by the APVMA form part of the state/territory control-of use regime. When the APVMA determines that off-label use of a product should be restricted, specific label instructions are included under a 'RESTRAINT' heading, for example: 'RESTRAINT: Not for use in food producing animals'. Restraints are enforceable under state/territory control-of-use legislation.[54]

4.53 Professor Barton described the controls currently in place in the Australian agricultural sector as 'very disappointing in that the lowest common denominator approach was finally used to get all the States and Territories on board'.[55] Professor Collignon also commented that the implementation of the recommendation relating to off-label use as being 'very slow and poorly done'.[56] Significant gaps in the implementation of the recommendation were also identified relating to restrictions on prescribing, prescribing for domestic animals and dispensing by compounding pharmacies.[57]

4.54 Professor Collignon also commented that since JETACAR, there have been new developments such as the development of the World Health Organisation list of 'critically important' antibiotics. Professor Collignon stated that community based epidemics of fluoroquinolone resistant E. coli infections and Extended Spectrum Betalactamase (EBSL) E. coli infections have occurred and that they are clearly related in part to the use of certain 'critically important' antibiotics in food animals especially in poultry.[58]

4.55 Professors Barton and Collignon both pointed to the use of ceftiofur as an example of poor implementation of the JETACAR recommendations. EAGAR had

53 Professor Matthew Cooper, *Submission 23*, p. 14.

54 Senate Rural and Regional Affairs and Transport Legislation Committee, Supplementary Budget Estimates 2012–13, *Answer to question on notice No. 250, Department of Agriculture, Fisheries and Forestry.*

55 Professor Mary Barton, *Submission 7*, p. 3.

56 Professor Peter Collignon, *Submission 34*, Appendix, pp 3–4.

57 Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials, *Committee Hansard*, 7 March 2013, p. 38; Professor Mary Barton, *Submission 7*, p. 3.

58 Professor Peter Collignon, *Submission 34*, p. 3.

recommended that a label restraint be put on ceftiofur, however, according to Professor Collignon this recommendation was ignored by the APVMA.[59] Professor Barton stated that this 'critically important antimicrobial' is now used in a wide range of animal species including pigs and poultry when it is only registered very specifically for treatment of respiratory disease and foot infections in cattle. It is also used for a wider range of conditions in cattle too.[60]

4.56 The Australia Institute also noted Professor Collignon's comments in relation to ceftiofur and stated that third generation cephalosporins such as ceftiofur are currently used in food animals being registered for cattle use and used off-label for pigs. Further:

> Professor Peter Collignon from the Australian National University has recently argued that he is not convinced by claims made by the poultry and cattle farming sector that the use of ceftiofur is minimal. He cites as reasons for his scepticism the lack of any rigorous surveillance and monitoring of use and resistance, as well as the fact that advertisements in trade magazines continue to promote inappropriate use of ceftiofur. A study in 2009 showed a quarter of Australian pig herds were given ceftiofur for treatment of diarrhoea.[61]

4.57 Professor Cooper expressed concern that third-generation or fourth-generation cephalosporins may be being used in veterinary medicine. While Professor Cooper did not have any direct evidence that these antibiotics are being used in animals, he argued that they should be taken off the schedule of veterinary use because of their extreme value in human medicine.[62]

4.58 The APVMA commented that the veterinary use of third generation cephalosporins is 'severely restricted'. Ceftiofur is the only veterinary medicine registered from this group and is available only on veterinary prescription. APVMA stated that it must be used according to 'strict restraints' including for individual animal treatment only.[63]

4.59 However, Professor Barton noted that jurisdictions vary in what veterinarians are allowed to prescribe with some allowing a wide discretion for veterinarians:

> In some jurisdictions veterinarians can prescribe and dispense whatever antimicrobials they like provided the use is not specifically prohibited. Provided an antimicrobial is registered for use in one livestock species in most situations vets can use that antimicrobial in all livestock species, even if it is not registered for use in that species.[64]

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59 Professor Peter Collignon, *Submission 34*, Appendix, pp 3–4.

60 Professor Mary Barton, *Submission 7*, p. 3.

61 The Australia Institute, *Submission 13*, pp 17–18.

62 Professor Matthew Cooper, *Committee Hansard*, 7 March 2013, p. 29.

63 Australian Pesticides and Veterinary Medicine Authority, *Submission 29*, p. 3.

64 Professor Mary Barton, *Submission 7*, p. 3.

4.60 Professor Cooper also indicated that veterinarians are allowed by law to 'off-label' with veterinarians permitted to exercise professional judgement in the off-label use or supply of most drugs or other veterinary medicines. He noted that this gives veterinarians access to beneficial drugs which may be registered for human use or which have limited registration for veterinary use.[65]

4.61 Off-label use of antimicrobials in aquaculture was another issue raised in evidence. In this case, evidence for the resistance to several important antibiotics has been found. The Australian Institute commented:

> [A]ssessment of the occurrence of resistance to antimicrobials in bacteria from aquaculture species and environments in Australia found resistance to a number of antimicrobials, including ampicillin, amoxicillin, cephalexin and erythromycin, oxytetracycline, tetracycline, nalidixic acid and sulphonamides. Multiple resistance was also observed.
>
> These findings indicate that, even though no antibiotics are registered for use in aquaculture, there has been significant off-label use. This has potential implications for human health when fish are eaten and farm run-offs contaminate the environment.[66]

4.62 In relation to domestic animals, Professor Barton commented that antimicrobials can be used off-label with no constraints at all in cats, dogs and horses.

4.63 A further concern raised by Professor Barton related to compounding pharmacies. These have only emerged since JETACAR. The APVMA has no control over them so that can legally formulate what they like, for example fluoroquinolones, which are used in horses. Professor Barton went on to state that that formulation is 'eminently suitable for use in other livestock species and in aquaculture. It is clear that from time to time vets illegally dispense some antimicrobials and the "free" availability from compounding pharmacies makes illicit use much easier'.[67]

4.64 DAFF indicated that proposed harmonisation of state and territory veterinary prescribing and compounding rights is an element of the current COAG reforms for a single national framework for the regulation of agricultural chemicals and veterinary medicines. DAFF, in partnership with the states and territories is developing models under this proposed framework for delivery to COAG by the end of 2012.[68]

Use of 'critically important' antibiotics

4.65 The concept of critically important antibiotics has been established. These critically important antibiotics provide a specific treatment, or one of a limited number of treatments, for serious disease. Some antibiotics are considered to be critically important for use in humans and others were considered critical only for use in animals, and some are considered to be critical for both humans and animals. The

65 Professor Matthew Cooper, *Submission 23,* p. 14.

66 The Australia Institute, *Submission 13, Attachment 1,* p. 22.

67 Professor Mary Barton, *Submission 7,* p. 3.

68 Senate Community Affairs Legislation Committee, Budget Estimates 2012–13, *Answer to question on notice No. E12–280, Department of Health and Ageing.*

antibiotics considered critically important for both humans and animals were considered to be priorities for resistance surveillance and for implementation of appropriate management measures to maintain the efficacy of the drugs.[69]

4.66 DAFF provided the following information on the antibiotics used in animals in Australia, including domestic pets, which are listed are 'critically important in human medicine' by the WHO:

Table 4.1: Antibiotics on the WHO 'critically important in human medicine' used in animals in Australia

Antibiotic class	Active constituent
Aminoglycosides	Gentamycin
	Streptomycin
	Framycetin sulphate

Source: Senate Rural and Regional Affairs and Transport Legislation Committee, Budget Estimates 2012–13, Answer to question on notice No. 269, Department of Agriculture, Fisheries and Forestry.

4.67 Professor Collignon commented that while fluoroquinolones have been banned, much better regulation of drugs defined as 'critically important' for human health by the WHO is required. He stated that:

> In my view, we need to ensure that these drugs are not used in food animals at all or if they are under much stricter controls than appear currently to be the case. This is very important for poultry, as poultry seems from international studies to be a disproportionate contributor to the carriage of resistant bacteria by people compared to other foods.[70]

4.68 Professor Grayson also commented that at the moment, Australia is not adhering to the WHO critical antibiotic list. Although most are banned in agriculture use, Professor Grayson stated that:

> We are pretty good but we are not right there, and I think we should be there. If we are going to achieve world-best practice we should be adhering to a very thoroughly researched document like that and saying: 'The drugs we're going to use in agriculture will be only those that are deemed to be suitable.[71]

Plant health

4.69 The committee was also informed of the use of antibiotics in plant health programs. In the USA about five per cent of antibiotics are used in plant health applications.[72] While a smaller part of the overall potential for causing resistance, it

69 Australia Lot Feeders' Association, *Submission 11*, p. 3; Joint submission by Cattle Council of Australia and Sheepmeat Council of Australia, *Submission 16*, p. 3.

70 Professor Peter Collignon, *Submission 34*, p. 3.

71 Professor M Lindsay Grayson, *Committee Hansard*, 7 March 2013, p. 11.

72 Goat Vet Consultancies, *Submission 33*, pp 3–4.

was suggested to the committee that plant health applications should also be considered for better regulation:

> Bee antibiotic use and honey residues are areas which are grey and not transparent. Plant Health Australia is responsible for bee health policy due to the importance of bees to plant fertilisation, but the APVMA have bees using veterinary medicines.[73]

4.70 Other areas of concern relating to plant health, included ethanol production and other fermentation processes. Goat Vet Consultancies pointed to a lack of regulation for such activities:

> Ethanol production industry overseas (and possible other fermentation industries) also use antibiotics and such use is not regulated either by APVMA as they do not register antibiotics used in manufacturing. In Australia, the responsibility for regulating the use of antibiotics in fermentation is uncertain as is the presence of antibiotic residue in fermentation by-products that are used for livestock feed. Currently there are no national standards for livestock feeds, although they have been in committee for a couple of years.[74]

4.71 The committee notes that in 2010, FSANZ undertook a risk assessment of imported apples from New Zealand harvested from trees potentially treated with an antimicrobial to control fire blight. It was concluded that there was negligible increased risk to Australian consumers from potential exposure to AMR organisms.[75]

Integration of regulatory arrangements

4.72 Submitters commented that effective and complementary regulation across human medicine, veterinary medicine and the agricultural sector is required to reduce indiscriminate use of antibiotics and to keep levels of AMR low in both humans and animals.

4.73 While it was noted by Associate Professor Gottlieb that goodwill and interest exists in reducing use of antibiotics, this was not enough: interest 'quickly dissipates when they are faced with day-to-day realities and individual patients, and antibiotics use often goes unchecked'. Associate Professor Gottlieb went on to comment that not only is education required but also 'true regulation of antibiotic use because goodwill and interest alone will not suffice'.[76] He also added:

> Ultimately, we feel that regulation is very important. Antibiotics need to be restricted, how they are used needs to be better controlled, and I fear that we particularly need to focus on non-medical use. I do not have the evidence of how much use there is—that is not my area—but I see some articles suggesting that it is substantial in other areas such as agriculture and

73 Goat Vet Consultancies, *Submission 33*, p 3.

74 Goat Vet Consultancies, *Submission 33*, pp 3–4.

75 Senate Community Affairs Legislation Committee, Supplementary Budget Estimates 2012–13, *Answer to question on notice No. E12–222, Department of Health and Ageing.*

76 Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials, *Committee Hansard*, 7 March 2013, p. 38.

> that we need to tightly regulate antibiotic use. There is so much evidence about how much resistance is coming across the food chain and we cannot ignore it.[77]

4.74 Submitters also called for the regulation of antibiotics in the human and animal sectors to be brought together or, at least, that mechanisms be put in place to ensure coordination.[78] Associate Professor Gottlieb commented:

> …regulation of how antibiotics are approved and used should be across human and other sectors. This could be done as one body. I cannot see why antimicrobials should be split apart between different interested groups.[79]

4.75 Dr Looke supported the creation of a central agency to coordinate drug usage. In addition, a central agency could distribute information as new trial evidence and new data becomes available. This would enable listings on the PBS to be updated:

> I think that all the agents that are used, right across, from human and veterinary medicine to agricultural use, all need to be in the same basket, so that we say: 'We have this drug. It is inappropriate to use this in animal medicine because you have got this instead, which is a different group of drugs, which we know, from evidence, does not promote resistance that can come through the food chain into humans.' We need to have that sort of overview of it. And then the PBS needs to reflect that.[80]

4.76 Dr Looke also argued that the creation of central agency would overcome the problem of relying on submissions by the original sponsor of a drug to trigger a review. He pointed to the European approach where agents are only licensed for a limited period of time. Once this has expired, new trial information, new data and new indications are submitted. These submissions may be made by people other than the original submitter.[81]

4.77 In this regard, Dr Looke noted some approvals go back to the 1960s and have never been reviewed by the TGA even though it may be of benefit to have greater restrictions placed on the use of some antimicrobials. Dr Looke commented:

> Our whole formula of antibiotics were approved by the TGA, often back in the 1960s, and have never been reviewed and gone through and looked at

77 Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials, *Committee Hansard*, 7 March 2013, p. 42.

78 Centre for Research Excellence in Minimising Antibiotic Resistance in Acute Respiratory Infections, *Submission 4*, p. 1; Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 16.

79 Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials, *Committee Hansard*, 7 March 2013, p. 38; see also Centre for Research Excellence in Minimising Antibiotic Resistance in Acute Respiratory Infections, *Submission 4*, p. 1; Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 16.

80 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 16.

81 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 17.

> again, simply because it is just too difficult, with the way the current system is set up, to go back and redo things without sponsors wanting to fund them. Of course, most antibiotics now are cheap drugs made by generic companies that are not going to go and fund that type of relook when the answer might be that the drugs should be more restricted in their use.[82]

4.78 The Antimicrobial Resistance Summit held in 2011 made recommendations in relation to regulation:

- resistance risk assessments should be part of the regulatory process for bringing new antibiotics to market for both humans and animals.
- the Pharmaceutical Benefits Advisory Committee should consider resistance in the criteria for inclusion or restriction of antibiotics on the Pharmaceutical Benefits Scheme.
- strategies should be implemented to enable 'fast-tracking' of important new antimicrobials through the regulatory approval system.
- strategies should be implemented to enable the registration of 'orphan' non-commercial drugs that have the potential to improve patient outcomes and reduce disease burden.
- adopting an antibiotic importance rating system as regulatory policy should be considered.[83]

Conclusions

4.79 The committee acknowledges that there are regulatory arrangements in place that control the use of antimicrobials. In particular, the committee notes the implementation of standard 3 of the NSQHS Standards which encourages appropriate use of antimicrobials in healthcare services. Healthcare services must have in place antimicrobial stewardship programs, monitor antimicrobial usage and resistance, and act to improve antimicrobial stewardship. The committee considers that this is an important step in reducing the overall use of antibiotics in Australia.

4.80 However, the committee also received comments in evidence that stewardship programs are not implemented thoroughly in certain circumstances. The committee considers that consideration needs to be given to further reform and coordination of use and access to antimicrobials in hospitals. In particular, access to and use of any new antibiotics which become available should be safeguarded for the future.

Recommendation 5

4.81 The committee recommends that the Australian Commission on Safety and Quality in Health Care consider mechanisms to improve coordination and tighten access to antimicrobials in healthcare services, particularly in relation to any new antimicrobials that become available.

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82 Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard*, 7 March 2013, p. 16.

83 Australia Society for Antimicrobials, *Submission 5*, p. 3.

4.82 The committee considers it may be possible that more attention needs to be paid to the prescribing practices of general practitioners. While much can be done through targeted education programs (which are discussed in chapter 6), the committee considers that other avenues should be explored to encourage better antibiotic stewardship by general practitioners.

Recommendation 6

4.83 The committee recommends that the Department of Health and Ageing investigate additional mechanisms to improve antibiotic stewardship in general practice.

4.84 In relation to concern with current regulatory arrangements for animal health, submitters were concerned that:

- Australia does not adhere fully to the WHO list of critically important antibiotics that should not be used in animals;
- although no longer described as 'growth promotion', the same type of antibiotic usage was thought to be occurring in food animals; and
- the emerging issue of the use of antimicrobials for plant health creates another potential path for the spread of AMR.

4.85 The committee considers that Australia should strictly adhere to WHO list of critically important antibiotics that should not be used in animals. This would not only address a significant concern about the use of these drugs but also enhance Australia's international leadership on AMR.

Recommendation 7

4.86 The committee recommends that consideration be given to banning all antibiotics listed as 'critically important in human medicine' by the World Health Organisation for use in animals in Australia.

4.87 The committee is particularly concerned about the weaknesses in the current regulations relating to the off-label use of antimicrobials in animals as well as the non-therapeutic use of antimicrobials in intensive agriculture and aquaculture.

4.88 Off-label use of antibiotics may be wide-spread. Submitters noted that JETACAR recommended that off-label use of antibiotics in animals be made an offence. However, off-label use is allowed in certain circumstances under state and territory legislation. Of particular concern was the use of third-generation cephalosporins. The committee notes that proposals for the harmonisation of state and territory prescribing and compounding rights is an element of the Council of Australian Governments' reforms for a single national framework for the regulation of agricultural chemicals and veterinary medicines.

4.89 There are moves overseas to ban the use of antibiotics as growth promotants. The evidence received by the committee indicates that the benefits of antibiotics as growth promotants is not as significant as it once was. Some industry groups have indicated that this practice is no longer undertaken in their industry. These industries are to be commended. However, it appears that other industries continue to use

antibiotics to improve growth in food animals. The committee considers that appropriate cost-benefit analysis should be undertaken to determine whether there are net benefits in allowing the practice to continue, given the costs and disadvantages arising from AMR. The cost-benefit analysis should be completed by a suitably independent body as an input into revised regulations for non-therapeutic use of antimicrobials in agriculture and aquaculture.

4.90 In addition, it was suggested to the committee that pharmaceutical companies may be seeking to redefine the term 'therapeutic' to include the routine use of antibiotics in disease prevention. While no evidence was provided that this had occurred in a widespread fashion, the committee notes that JETACAR considered that if antibiotics are given in the same way as growth promoters, proper regulatory evaluation should be undertaken.

4.91 The committee did not receive any evidence on the extent to which antibiotics are used for either prophylactic use (to prevent disease) or therapeutic use (to treat disease once it has occurred). The committee considers that more investigation of use of antibiotics for prophylactic use or therapeutic use is required.

4.92 The lack of integration between the regulations relating to the use of antimicrobials by humans and animals was a significant issue in this inquiry. As Professor Grayson noted 'agriculture and human health are linked. The bugs are the same. They do not care whether it is a cow or a human; it is just a different species.'[84] The committee considers that integrated regulations for AMR should also have a particular focus on ensuring human and animal medicine are both addressed in a consistent and complimentary fashion.

4.93 During the inquiry the committee also heard a range of other suggestions for better regulation. The committee considers that the following points are worthy of further consideration in developing an integrated AMR regulatory system:

- changing the arrangements for reviews of licences for antimicrobials so that the license can be time-limited and reviews can be triggered by means other than a submission by the original sponsor;
- requiring resistance risk assessments for bringing new antibiotics to market for both humans and animals;
- enabling 'fast-tracking' of important new antimicrobials through the regulatory approval system;
- enabling the registration of 'orphan' non-commercial drugs that have the potential to improve patient outcomes and reduce disease burden;
- using antibiotic importance ratings; and
- implementing resistance criteria for inclusion of antimicrobials in the Pharmaceutical Benefits Scheme.

84 Professor M Lindsay Grayson, *Committee Hansard*, 7 March 2013, p. 9.