



## Microbiology and Infectious Diseases Unit

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Submission to Senate Enquiry

“Inquiry into the progress and implementation of the recommendations of the 1999 Joint Expert Technical Advisory Committee on Antibiotic resistance (JETACAR)”

Parliament House

CANBERRA. ACT. 2600

Dear Senators

Rising antimicrobial resistance is a very important issue and needs more recognition on what a potential threat it is to all Australians. Antibiotic usage and resistance needs much better monitoring and controls - both within Australia and internationally.

Antibiotics are truly one of the “Miracle drugs” of the 20<sup>th</sup> Century. Before they were available, people in the 1920’s and 1930’s when suffering from serious infections caused by bacteria such as Staphylococcus aureus (Golden Staph) or the pneumonia bacteria (pneumococcus) had an 80% mortality within 30 days with bloodstream infections. This mortality was markedly decreased by the use of antibiotics and remains so in Australia.

Unfortunately when antibiotics are used antibiotic resistance inevitably develops and spreads. The more antibiotics that are used, the more resistance eventually develops. This spread is made worse in the healthcare sector if there is also less than optimal infection control procedures followed and when more susceptible people are crowded together. These latter factors allow resistant bacteria (“Superbugs”) to spread more easily from person to person.

In the community Superbugs can also be acquired and can spread from person to person. When there are foods and/or water contaminated with resistant bacteria, these Superbugs will spread to people in their homes. Fortunately in most of Australia we have safe water supplies and so contaminated water is not a major issue in our country in comparison to many developing countries. Food however is a vehicle here for transmitting resistant bacteria to people. Another issue is environmental contamination with resistant bacteria. Antibiotics are widely used in both people and food animals. This can result in large amounts of antibiotic residues as well as resistant bacteria and their antibiotic genes being deposited in waterways and the environment. This then increases the chance that other bacteria will pick up these resistant genes and “new” resistant bacterial strains will develop and then potentially spread to people or animals.

However in Australia with people the major issue in the development and spread of resistant bacteria is the type of antibiotics that are used and the volume of antibiotics. Australia is a relatively high use antibiotic country for people compared to many Scandinavian countries and the Netherlands. We need to do better to both restrict the total volumes of antibiotics used and more particularly the volumes of broad spectrum antibiotics used both in the community and in hospital settings. This will require a combination of both improved data collection and education but also improved regulations - and enforcement of those regulations.

The other very important sector is the agricultural industry. Both in Australia and worldwide about 70% of all antibiotics that are used are consumed in food animals and most of these are with antibiotics

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in classes that are also used in people (but confusingly the names of individual drugs are quite different in the two sectors). Given that the biggest drive for resistance is the volumes of antibiotics used, this is obviously very important. More specifically 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. What is worse is that there is now ample evidence that this leads to needless increased deaths in many people as well as increased suffering in many people.

A major use (or more correctly an “abuse”) of antibiotics internationally is the large volumes used as “growth promoters”. When one has conditions of poor animal husbandry, then antibiotics may have some effect at helping to produce a small increase in animal growth. However when animals are raised in good conditions, then there is no or little benefit from the use of these antibiotics, other than possibly a slight improvement in their feed conversion. This latter point means that animals might eat about 1% less food to gain the same weight compared to not being on antibiotics. Extensive data from Denmark with poultry and pigs and also from a US poultry producer have shown that there is no improvement in animal welfare or mortality by the use of routinely adding antibiotics in feed or in water. Nor do these antibiotics decrease disease. Most importantly they also do not result in weight gain when the few very large studies ever done on this issue are examined. However this practice with its poor economics from a farming perspective does produce large numbers of resistant bacteria in those food animals and those Superbugs are transmitted to people. This is a needless risk that people are constantly exposed to.

In food animals antibiotics are also used in large volumes routinely as “prophylaxis” (or disease prevention). When whole herds are exposed to this practice it is called “metaphylaxis”. The data that this is of any significant long term benefit to animals or food production is also poor. What is a concern with the pharmaceutical industry, is that now that there are major international moves to ban the use of antibiotics as “growth promoters” they have redefined the word “therapeutic” so that this term now also encompasses the routine use of antibiotics as prevention or prophylaxis. 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.

In human medicine we would not dream of giving large proportions of the population routine antibiotics continuously as prophylaxis and calling that practice “therapeutic”. First of all it would not work at preventing any infections or diseases that I could think of and secondly it would cause huge increases in antibiotic resistance. Why this is still allowed in the food animal industry I think is a major problem. Why are there such different rules for agriculture compared to what we expect in human medicine? This large scale unnecessary use of antibiotics causes damage to the agriculture industry itself (because there are then more resistant bacteria in these food animals than there needs to be and thus when they become ill there are less options to treat those animals). However more importantly, there is good evidence that these resistant bacteria that develop in food animals come through the food chain, are carried by people and then cause serious infections in people.

In the Netherlands currently between 25-50% of the E. coli superbug (extended spectrum beta-lactamase or ESBL – and which is resistant to all 3<sup>rd</sup> generation cephalosporins) is causing serious disease including blood stream infections in people and appear to be derived in large part from poultry sources. In many countries all meat chickens just before or after hatching are injected with a 3<sup>rd</sup> generation cephalosporin. This antibiotic (ceftiofur) can also be sprayed on chickens for a period after they are hatched. From my estimates there is likely an increase in hundreds of deaths in Europe per year because of the practice of just using this one drug, a third generation cephalosporin (ceftiofur) in poultry. That same drug is used in Australia in beef and pork (and likely off-label uses in other animals). In addition to this dangerous practice, in many countries fluoroquinolones (e.g. enrofloxacin) are added routinely to the water or feed of many food animals for a large proportion of their lives.

Because of this ESBL E.coli problem from poultry and also because of the MRSA strains that have developed in their pork industry and spread to people there, The Netherlands government has recently passed legislation that required a at least a 50% reduction in total volumes of all antibiotics used in

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their food animal sector. My understanding is that a 70% reduction looks like it will be achieved later this year compared to the previous peak usage. In addition this reduction seems to have occurred without any obvious detrimental effect on animal production of welfare, and highlight how much “waste” there was with the use of these huge volumes of antibiotics. The only group that seems to have benefited from this huge overuse were the large Pharmaceutical companies that produced and supplied these drugs (ego Pfizer with ceftiofur and Bayer with enrofloxacin). Denmark has also previously achieved a large reduction in total antibiotic usage in food animals compared to when growth promoters were previously permitted.

Fortunately Australia is in a much better position than most other countries around the world re some types of very worrying resistant bacteria. We need however to do more to keep it that way and improve on what is happening now. The good news for Australia is that one of the group of drugs that is a major problem worldwide (fluoroquinolones) were never approved for use in food animals in this country and are therefore effectively banned. This has resulted in Australia having one of the lowest fluoroquinolone resistance rates in the world in important bacterial pathogens for people (salmonella, campylobacter, E.coli) despite over 30 years of use for these types of drugs in people. Another important factor is that we have moderately effective controls on the use of this group of antibiotics in people (by our Pharmaceutical Benefits Scheme and the need to have an authority for a lot of these drugs). The other important factors are that we have relatively a very safe water supply in this country and that we do not import raw meats into this country.

Our poultry industry has not allowed the use of 3<sup>rd</sup> generation cephalosporins here in meat chicken production.

While we have a very good example regarding fluoroquinolones in this country (see attached published peer reviewed article on this issue), we need much better regulation of drugs defined as “critically important” for human health by the WHO. 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.

Australia has one of the lowest rates of antimicrobial resistance to important pathogens such as E. coli in the world re bacteria that likely come through the food chain and I think we need to do our best to keep it that way.

There are arguments by some in industry that one cannot have a competitive industry without the widespread use of antibiotics. I would like to point however that we are one of the biggest beef exporters in the world and most of our beef relatively see little in the way of antibiotics for most of their lives. This is because effectively we have most of our beef produced in open pastures (or effectively free range) and those that go to cattle feed lots they spend limited times in those cattle feed lots. Denmark is the biggest pork exporter in the world and it does this with about a 20<sup>th</sup> of the amount of antibiotic used per kilo of pork produced than is the case in the US. Thus Australia and Denmark are examples of very effective exporters of meat products who are able to do it without the large scale use of antibiotics compared to many other countries in the world. In addition there is one large food chain in the US that now has signs in their fast food restaurants pointing out they source their meats from producers who do not use antibiotics.

JETACAR in its report concluded that resistant bacteria develop and come across to people via the food chain. It made a numbers of recommendations. Most recommendations have not been carried out or it has been done in my view only half-heartedly. What we have now more than 10 years later is much better data showing how this problem is getting worse. We also have new developments since then such as the WHO list of “critically important” antibiotics and internationally, community based epidemics of fluoroquinolone resistant E.coli infections and ESBL E.coli infections that are clearly related in part to the use of certain “critically important” antibiotics in food animals especially in poultry. JETACAR made many recommendations that addressed the issues and these need to be implemented (see appendix for more specific details on each JETACAR recommendation).

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Thus in summary to really control antimicrobial resistance we need to look at all sectors where antibiotics are used or are deposited - the human sector, agriculture and in the wider environment. There are countries for instance where antibiotics are sprayed onto apples for bacterial diseases. There are also important issues with waterways that can be contaminated with both drugs and resistant bacteria. We need to look at trade issues and be very careful that we are not importing contaminated meats, fish, vegetables or other products into this country that contain either resistant bacteria or drugs because the processes used in other countries are much less than what we expect and enforce on farmers in this country. A major factor in having lower levels of resistant Salmonella, Campylobacter and E. coli in this country has been for agricultural quarantine reasons the lack of importation of uncooked meats into this country, particularly poultry but also beef and pork. At the end of the day we need major reductions in the volumes of antibiotics used in both people and food animals. We also need to do all we can to also make it difficult for any “superbugs” that develop to not be spread by direct contact or via food and water. We also need to reserve some last line antibiotic class (those defined as “critically important to human health) for human use.

Yours sincerely

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(Feb 14<sup>th</sup>, 2013)

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## Appendix

Recommendations and my interpretation on whether these recommendations have been followed.

JETCAR conclusions and recommendations;

These all remain valid today.

### **Overall conclusion**

JETACAR considered the whole area of the occurrence of antibiotic resistance and its importance in human and veterinary medicine. The committee agreed that there was evidence for:

- the emergence of resistant bacteria in humans and animals following antibiotic use;
- the spread of resistant animal bacteria to humans;
- the transfer of antibiotic-resistance genes from animal bacteria to human pathogens; and
- resistant strains of animal bacteria causing human disease.

Recommendation 1;

#### *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.

In my view this recommendation has never been effectively implemented. There are still large amounts of antibiotics that are being effectively used in this way in Australia now despite this recommendation. Only virginiamycin has had any evaluation done. That was slow and still means large volumes of this drug are used.

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

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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.

This recommendation has not been adequately followed.

No investigation of avoparcin was ever finalized and published by the NRA. This was said to be because Roche withdrew it from the market. However this meant that the NRA never did a formal evaluation to find that avoparcin caused VRE to develop and this spread to the human population. Thus we have nothing on the public record by a regulator that an antibiotic growth promoter caused the development and spread of the "superbug" VRE to humans.

Streptogramin investigation took many years to complete and then was held up in AAT appeals for even longer.

Still no Macrolide evaluation has been satisfactorily done and published to my knowledge.

### Recommendation 3;

#### *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.

This does not appear to have been done.

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## Recommendation 4;

### *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 (see Appendix 4).

This seems to have been done. However drugs that are currently a major concern e.g. cefiofur were on the market before this and so seems to have escaped being captured by these sensible recommendations.

## Recommendation 5;

### *Recommendation 5*

That a recognised expert authority (the Working Party on Antibiotics or its successor) defines threshold (or trigger) rates of resistance for antibiotics registered for use in animals and circumstances where usage should be investigated and mitigation proceedings instigated where appropriate. In addition, resistance prevalence data should be included in the product information and this information should be updated on a five-yearly basis.

This has been only poorly followed. Whatever committees or working parties that were set up were poorly resourced and were often disbanded and then started again in areas (e.g. NHMRC) where it was not clear what they should do or were empowered to do.

## Recommendation 6;

### *Recommendation 6*

That all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only).

This has still not been followed for all antibiotics. In addition another major issue is that Veterinarians are allowed to sell antibiotics in this country. If control on usage is needed then the people prescribing antibiotics should not also be allowed to sell those antibiotics. This is the case for medical practitioners and people and should be the same for wherever antibiotics are prescribed and sold.

## Recommendation 7;

### *Recommendation 7*

That the Agricultural Resource Management Council of Australia and New Zealand implement a harmonised approach by all States and Territories in Australia (including clarification of responsibilities) to the control of use of veterinary chemicals, including antibiotics.

I am not sure if this has been done.

## Recommendation 8;

### *Recommendation 8*

That, following the implementation of Recommendation 7, the relevant State and Territory health/agriculture/primary industries legislation is amended to make it an offence to prescribe and/or use a veterinary chemical product contrary to a National Registration Authority (NRA) label restraint, unless authorised to do so by an NRA permit.

This has been very slow and poorly done. Despite EAGAR (a working party on antibiotics) recommending that a label restraint be put onto ceftiofur many years ago that advice was ignored by the regulator - our APVMA (which was the renamed NRA). This same issue occurred in the USA with the FDA and after many years there is now finally there a label restraint. It is unclear to me still on what

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restraints are placed on the use of ceftiofur here or on other similar drugs. There seems to be a lot of off-label use of ceftiofur. Also it is unclear if states or the commonwealth can enforce any restraint. If it is the states that means for practical purposes there will be relatively little supervision and controls on what is occurring that might be illegal.

## Recommendation 9;

### *Recommendation 9*

Similar to recommendations made in veterinary medicine, it is recommended that the Therapeutic Goods Administration (TGA) implement the following:

- inclusion of microbial resistance safety data, including the propensity for promoting resistance and cross-resistance, as a basic requirement of the assessment of all new antibiotics by the TGA, with adoption of similar data requirements to those required in the registration of veterinary antibiotics (Recommendation 4);
- definition by a recognised expert authority (Working Party on Antibiotics or its successor) of the threshold rates of resistance to registered human antibiotics and circumstances where usage should be investigated and mitigation procedures instigated where appropriate; and
- inclusion of national human antibiotic-resistance prevalence data in the product information and updating on a five-yearly basis.

This has been done poorly and only in part.

## Recommendations 10 and 11;

### *Recommendation 10*

That a comprehensive surveillance system be established incorporating passive and active components measuring incidence and prevalence of antibiotic-resistant bacteria and resistance genes, covering all areas of antibiotic use. To achieve this aim, it is further recommended that a multidisciplinary taskforce of relevant experts be formed by the federal ministers of health and agriculture to design, cost and recommend funding mechanisms and management systems for reporting and analysis of antibiotic resistance data in Australia.

The overall surveillance system should include medical (including nosocomial), food-producing animal and veterinary areas, with particular emphasis on the establishment of food-chain (including imported food) and environmental connections, and include molecular studies of resistance genes. The efforts of the taskforce should be directed at adopting a uniform, systematic and synergistic approach across all areas by utilising, enhancing and extending currently available systems and organisational structures.

### *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.

These recommendations (10 and 11) have been done poorly and only in patches. We have nothing in place like the Danish, Swedish, Norwegian, Netherlands or Canadian systems. The EU as a whole puts

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out more regular and updated data than does Australia, despite its many member countries that need to supply the data.

## Recommendations 12-14;

### *Recommendation 12*

That 'hazard analysis critical control points' (HACCP)-based food safety procedures be implemented as a means of reducing the contamination of food products with foodborne organisms, including antibiotic-resistant organisms and that these programs also address on-farm infection control.

### *Recommendation 13*

That where the intensive animal industries (such as meat chicken, pig, feedlot cattle and aquaculture) currently depend on the use of antibiotics to improve feed conversion and prevent and treat disease, cost-effective nonantibiotic methods to increase productivity and prevent disease should be developed by these industries. In relation to this, it is further recommended that the federal ministers of health and agriculture explore additional funding alternatives for this work, taking into account the current efforts of the animal industry research and development organisations.

### *Recommendation 14*

That the Department of Health and Aged Care examine current surveillance activities for hospital-acquired (nosocomial) infections, particularly for antibiotic-resistant strains; and that the department work with stakeholders (including the States and Territories) to further develop a comprehensive and standardised national system for monitoring nosocomial infections that will facilitate:

- earlier recognition of a public health problem;
- improvements in infection control and hygiene measures; and
- the timely development of national standards, guidelines and practices for both surveillance and infection control in the health care setting.

These recommendations have been done poorly and only in patches.

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## Recommendations 15-17;

### *Recommendation 15*

That prudent use codes of practice for antibiotics be developed and regularly updated by medical and veterinary peak bodies, including learned societies, professional organisations, producer organisations, pharmaceutical companies and State/Territory medical and veterinary registration boards, and promulgated to their members. These codes of practice should be based on the principles articulated in this report.

### *Recommendation 16*

That regularly updated 'antibiotic use guidelines', both human and veterinary, supported and endorsed by the appropriate professional organisations, the pharmaceutical industry and the federal and State

and Territory departments of health and agriculture, are widely disseminated and adopted as a 'standard of care' by training institutions, and established as the benchmark for undergraduate and postgraduate teaching. The effectiveness of the 'antibiotic use guidelines' in ensuring prudent prescribing of antibiotics needs to be evaluated every five years.

### *Recommendation 17*

That, as a priority, learned (medical and veterinary) and professional societies develop continuing educational programs on the issue of antibiotic resistance, including a focus on the prudent use principles, antibiotic use guidelines and alternatives to antibiotic usage.

Implementation has been patchy and slow. There are now major moves to improve what is happening in the human sector with antimicrobial stewardship however by the Australian Quality and Safety commission with the support and involvement of our Chief Health Officer.

## Recommendation 18;

### *Recommendation 18*

That all relevant research funding agencies be asked to give priority to research into antibiotic resistance, including:

- alternatives to antibiotics for growth promotion;
- alternatives to antibiotics for prevention and treatment of infections (including vaccines);
- molecular epidemiology and mechanisms of gene transfer;
- population dynamics of antibiotic resistance;
- resistance epidemiology;
- pharmacoepidemiology;
- efficacy of interventions to reduce antibiotic prescribing and use;
- clinical efficacy studies; and
- rapid diagnostic tests.

Implementation has been patchy and slow.

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## Recommendation 19-20;

### *Recommendation 19*

That an ongoing funded education strategy be developed by the relevant federal/State/Territory departments with input from stakeholders to provide appropriately targeted information about infection, the role and benefits of prudent antibiotic use and the risks of overuse to the public, relevant professional bodies and stakeholders.

### *Recommendation 20*

That a recognised expert authority (the Working Party on Antibiotics or its successor) assume responsibility for ensuring and coordinating the communication of data on antibiotic usage and prevalence of resistant bacteria to the public and other relevant stakeholders on a regular basis, taking into account the sensitivities of trade and other international implications.

Implementation has been patchy and slow. Groups such as AGAR are helping in the human sector but more extensive real-time data is also needed.

What has been done in the agriculture sector with food animals and foods has been intermittent and patchy.

## Recommendation 21;

### *Recommendation 21*

It is recommended to the ministers of health and agriculture that:

- the current functions and membership of the Working Party on Antibiotics (WPA) be expanded to carry out the antibiotic risk management program outlined in earlier recommendations;
- the administrative and reporting arrangements of the WPA (or its successor) be clarified so it can maintain its independent position and advise the Therapeutic Goods Administration (TGA) and the National Registration Authority (NRA) and other agencies/statutory bodies as required;
- the coordination of the antibiotic risk management program across government portfolios and industry be provided with secure recurrent funding for the additional tasks outlined in Recommendations 1 to 20;
- the WPA or its successor keep the regulatory framework for the use of antibiotics in human and veterinary medicine and food-producing animals under review and make appropriate recommendations to the regulatory authorities to review the uses of particular antibiotics, taking account of
  - the importance of the drug or class of drug in human and veterinary medicine, and
  - the potential for human exposure to antibiotic-resistant bacteria acquired from food-producing animals that are human pathogens or that can transfer their antibiotic-resistance genes to human pathogens;
- the WPA or its successor, the National Registration Authority and the Therapeutic Goods Administration develop appropriate procedures to ensure accountability and transparency of its activities, including established time-frames for reviews;
- the WPA (or its successor) develop a five-year strategic plan and an annual budget for its activities; and
- the operations of the WPA (or its successor) be subject to a five-year independent review program.

What has been done is patchy and intermittent.

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## Recommendation 22;

### *Recommendation 22*

That the Department of Health and Aged Care convene a working group to develop a fully coordinated resistance management plan for human antibiotics, incorporating the elements included in Recommendations 9, 10, 11, 14, 15, 16, 17, 18, 19 and 20. The plan so developed should be incorporated into the recommended functions of the Working Party on Antibiotics or its successor (see Recommendation 21).

This does not appear to have been done.

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