



# THE CANBERRA HOSPITAL

Infectious Diseases Unit and Microbiology Department

A.C.T. Pathology

Canberra Clinical School - Sydney University

PO Box 11, WODEN ACT 2606. AUSTRALIA



Sydney University

**Peter Collignon.** M.B., B.S., B.Sc(Med), FRACP, FRCPA, FASM  
Clinical Associate Professor, Department of Infectious Diseases  
Provider No: 480673Y

phone 02 6244 2105  
fax (local) 02 62810349  
fax (international) 61 2 62810349

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Dockets Management Branch (HFA 305)  
Food and Drug Administration  
5630 Fishers Lane, Room 106,  
Rockville MD 20852 USA

Dear Sir

I reviewed your recent guidance for industry document (#152) "Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern". I think the document is well presented. It has gone through many well thought out processes to try and detail risk and define this risk as low, medium and high. It gives objective criteria on how to reach these points.

My background is as a medical practitioner in the areas of Infectious Diseases and Microbiology. I am involved with treating and diagnosing infections in people and have a clinical and research interest in antibiotic resistance and have been a vocal critic of the many misuses of antibiotics in animal husbandry and medicine.. There have been a number in the pharmaceutical industry producing antibiotics for animal use who have regarded some of my comments previously as being too restrictive on their industry. Therefore it is somewhat paradoxical that one of my main concerns about the FDA document is that I think the classification of the antibiotics based on their use in human medicine is too restrictive. The effect of these classifications is that any restrictions that result from this may make it harder for veterinary surgeons to treat infections with what may be the most appropriate antibiotics. I should stress however that my comments are referring to the therapy of animals. My view is that antibiotics should not be used as growth promoters (and also not to any large extent for prevention). All growth promotion use is in my view unnecessary, but despite this very high volumes are used for this purpose internationally. The therapy of sick animals is different, if a veterinary surgeon has made a diagnosis and decided that antibiotic therapy is indicated. The volumes needed to treat animals with a bacterial infection during a limited time, are much smaller than when antibiotics are routinely and continuously are fed to animals. I believe that all antibiotic use in food animals should be under the supervision of a veterinary surgeon and as in people should be controlled by the need for a prescription.

I attach below an updated table I have previously been involved with preparing as part of an assessment for a committee (JETACAR) that reported to the Australian Government (to the Departments of Health and Agriculture). In this you will see that many of the classifications for antibiotics are very similar to your classifications given in Appendix A of the FDA document. However, there are a number of notable differences. One of these is penicillin. Even though you have classified it as a 'high' importance to human health, my belief is that it should be classified much lower than this. My rationale for that is that even though this remains an important drug for the therapy of many infections (e.g. streptococcal disease), if resistance does develop there remain many alternatives that we can successfully treat people who are sick with these infections. My belief is that it is preferable to use narrow spectrum agents such as penicillin in the therapy of people and animals, rather than broad-spectrum agents such as third generation cephalosporins. However because the FDA has put penicillin in the same categorisation as a third generation

cephalosporin, I think this is likely to defeat a lot of the messages on the prudent use of antibiotics. When simple and narrow spectrum agents (e.g. penicillin) are categorised the same as broad-spectrum agents (e.g. third generation cephalosporins) this gives the wrong message and also I do not believe reflects the current microbiological opinion. On this rationale I also do not believe that amino-penicillins (such as ampicillin) should be classified as 'high' importance.

There is a similar problem with quinolones. I do not believe all quinolones should be classified the same way. Fluoroquinolones are of much more importance in human medicine than earlier generation quinolones. I therefore believe nalidixic acid should be classified at most as 'medium'. I should reiterate however that I fully endorse the proposal of the FDA to classify fluoroquinolones as of 'high' importance.

There is a similar problem with aminoglycosides. From my perspective in human medicine, amikacin is the main agent that I would regard as of high importance (and possibly netilmicin). For most of the other agents if resistance does develop we still have alternative (usually amikacin) available for therapy. Specifically I don't believe tobramycin and streptomycin should be classified as 'high' importance if antibiotic resistance is the principal problem we are concerned about in developing these classifications.

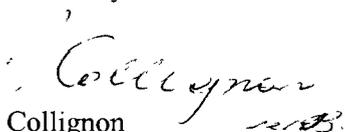
I think another very large area that is problematic is the macrolides and ketolides. While it is true that these agents are very important for therapy of some human infections such as mycoplasmata and *Legionella*, for most other infections which are more common (e.g. *Staphylococcus aureus*) there are many other alternative agents available if resistance develops. I therefore believe for the majority of human infections that macrolides could be classified as either "medium" or of "low" importance. I think the other point of note is that for many of the organisms where macrolides might be classified as of high importance (eg *Legionella* infection), there does not appear to be evidence that these organisms are likely to be acquired via the food chain and/or to acquire resistance from the use of these agents in animals.

The same comment I believe is also true for trimethoprim/sulfamethoxazole. These agents in medicine in developed countries are generally regarded as the second line and there are very few conditions where it would be regarded as of high importance. *Pneumocystis carinii* in HIV patients may be one exception but again this is a very small amount of the total use of this agent and food animals are no reservoir of this micro-organism.

My concern is that if we classify an agent as of 'high' importance, there should be significant restrictions on its use in animals (my preference would be that these agents are not used at all). My main exception to this would be if there were microbiology culture results that showed that no other simpler agent would have been efficacious in an individual animal. If we classify so many of these antibiotic classes as 'high' importance as has occurred in your Appendix A, we may well find the paradox develop that the really important new agents (eg linezolid) are classified the same as simple agents such as penicillin and trimethoprim/sulfamethoxazole. To my opinion this may be in the long run very detrimental because arguments will then be made that there should be no more restrictions on linezolid compared to macrolides and penicillin.

I realise the classifications of these antibiotic classes are problematic. Overall I believe there are classes of antibiotics that should be reserved for exclusive human use or if used in animals under very, very strict controls. I believe however there should not be too many agents added to this restricted list (that is the "high" importance list).

Yours sincerely



Peter Collignon  
Infectious Diseases Physician  
And Microbiologist

**"Categorisation and Summary of importance of different types of Antibiotics in Humans in Australia"**

Antibiotic	Category *	Use in Human Medicine
<b>Narrow-spectrum penicillins</b> Benzylpenicillin (pen G) and Phenoxymethylpenicillin (pen V)  Procaine and benzathine penicillins	Low  Low	Active against gram-positives (eg streptococci, enterococci, syphilis) and some anaerobes Short acting  Longer acting (intramuscular injection)
<b>Moderate-spectrum penicillins</b> Aminopenicillins (amoxicillin, ampicillin)	Low	Also active against GNRs (some <i>E coli</i> , <i>Klebsiella</i> ) plus <i>Haemophilus influenzae</i> . Destroyed by staphylococcal $\beta$ -lactamase enzymes
<b>Antipseudomonal penicillins</b> Piperacillin, ticarcillin	High	Similar to amoxicillin but have antipseudomonal activity and some additional gram-negative activity, eg <i>Klebsiella</i> .
<b><math>\beta</math>-lactamase inhibitors</b> Clavulanate, tazobactam	Med	Used in combination with amoxicillin, ticarcillin, and/or piperacillin to prevent $\beta$ -lactamase destruction of partner compound (eg amoxicillin against <i>S aureus</i> )
<b>Antistaphylococcal penicillins</b> Dicloxacillin, flucloxacillin, cloxacillin, methicillin	Med	Effective treatment against most strains of <i>S aureus</i> . Not destroyed by staphylococcal $\beta$ -lactamase.
<b>Cephalosporins</b>		Widely used broad-spectrum antibiotics (often in surgical prophylaxis) No activity against enterococci (unlike amoxicillin) or against MRSA
<b>1<sup>st</sup> generation</b> Cephalexin, Cephalothin, cephazolin	Med	Similar activity as amoxicillin but also active against staphylococci and better against GNRs ( <i>E coli</i> , <i>Klebsiella</i> )
<b>2<sup>nd</sup> generation</b> Cephmandole, cefotetan, cefaclor, Cefoxitin, cefuroxime	Med	Slightly increased activity against GNRs. Some activity against anaerobes.
<b>3<sup>rd</sup> generation</b> Cefotaxime, ceftriaxone	Med	Slightly increased activity against GNRs, less against staphylococci. Main advance is in treatment of meningitis.
<b>4<sup>th</sup> generation (anti pseudomonal)</b> Ceftazidime, ceftipime, cefepime	High	Similar to 3 <sup>rd</sup> generation except also antipseudomonal activity (sometimes therefore called 4 <sup>th</sup> generation)
<b>Carbapenems</b> Imipenem, meropenem, ertapenem	High	$\beta$ -lactams with broadest cover. No activity against MRSA or VRE, poor activity against <i>Stenotrophomonas</i> . Most GNRs are sensitive but some (eg <i>Pseudomonas</i> ) can develop resistance
<b>Monobactams</b> Aztreonam	High	Little use in Australia. Only active against GNRs. Mainly used in people with $\beta$ -lactam hypersensitivity.
<b>Aminoglycosides/ aminocyclitols</b> Neomycin Gentamicin, tobramycin Netilmicin, amikacin Spectinomycin	Low Med High Med	Aminoglycosides are the most predictively active agents against aerobic GNRs (however they are also more toxic than many other antibiotics) No activity against strep, enterococcus or anaerobes. Amikacin is the most stable against inactivation by bacteria. Spectinomycin is used infrequently for gonorrhoea.
<b>Tetracyclines</b> Demeclocycline, doxycycline, Minocycline, tetracycline	Low	Mainly 2 <sup>nd</sup> line agents. Useful for atypical infections, eg mycoplasma, chlamydia, where there are few suitable substitutes (cat A for those infections)
<b>Sulfonamides-trimethoprim</b> Sulfadiazine Trimethoprim, trimethoprim-sulfamethoxazole (co-trimoxazole)	Low Low	Mainly 2 <sup>nd</sup> line agents. Many bacteria remain sensitive to them. Trimethoprim often used alone as less side effects Very high resistance in bacteria such as pneumococci but still recommended drug for respiratory infections in many developing countries (cheap). Drug of 1 <sup>st</sup> choice for some conditions (pneumocystis, nocardia).
<b>Oxazolidinones</b> linezolid	High	Last new class of antibiotics developed. Major advance for the treatment of multi resistant enterococci (VRE) and staphylococcal infections. May be only active antibiotic currently available for some infections
<b>Macrolides</b> Azithromycin Clarithromycin Erythromycin, roxithromycin	High High Low	Mainly for gram-positive infections (esp staphylococcus and streptococcus) but resistance is increasing First choice for some conditions (legionella, mycoplasma, chlamydia) (ie High category). Clarithromycin and azithromycin (high category) for atypical mycobacteria

Antibiotic	Category *	Human Use
<b>Lincosamides</b> Clindamycin Lincomycin	Med	Similar to macrolides
<b>Glycopeptides</b> Teicoplanin Vancomycin	High	Last resort for many gram-positives including MRSA and for enterococci in allergic patients
<b>Nitroimidazoles</b> Metronidazole, tinidazole	Med	Very active against anaerobes (most predictable activity and least resistance) Also active against protozoans (eg giardia) which have few other options for therapy.
<b>Quinolones</b> Nalidixic acid	Med	Active against most GNRs.
<b>Fluoroquinolones</b> Ciprofloxacin, enoxacin Norfloxacin Ofloxacin (topical), moxifloxacin, gatifloxacin, levofloxacin	High High High	One of last major new classes of human antibiotics. Very active against GNRs, including some with no other oral treatments (eg pseudomonas, enterobacter). May be only active agent against multiresistant Klebsiella or <i>E.coli</i> . Poor activity against strep (latter released agents have improved activity). Poor activity against anaerobes (except moxifloxacin).
<b>Streptogramins</b> Quinupristin with dalbapristin	High	Relatively new class for human medicine. However resistance is intrinsic in some bacteria (eg <i>E.faecalis</i> ). May be only therapy available for some multi-resistant gram positive infections.
<b>Antimycobacterials</b> Pyrazinamide, streptomycin, Rifampicin, rifabutin, isoniazid, Ethambutol, Capreomycin, cycloserine	High	Effective against tuberculosis but resistance is a problem and 2 <sup>nd</sup> line drugs (which are more toxic) now have to be used again in some cases.
<b>Antileprotics</b> Clofazimine, rifampicin Dapsone	High High	Very effective against leprosy but resistance is a problem, especially if drugs not taken correctly
<b>Polypeptides</b> Bacitracin, capreomycin, Colistin, gramicidin, Polymyxin B, thiostrepton	Low	Colistin (polymixin) useful for topical therapy of pseudomonas. Occasionally used systemically if multiple resistance occurs but toxic.
<b>Miscellaneous</b> Chloramphenicol	Med	Broad-spectrum activity for respiratory tract infections and useful for oral therapy of meningitis but little use in developed countries (because of small risk of bone marrow toxicity). Widespread use in developing countries (cheap). Only used for urinary tract infections, many other substitutes.
Hexamine hippurate, Nitrofurantoin	Low	
Sodium fusidate	High	Fusidic acid has good antistaphylococcal activity. Usually used in combination therapy with rifampicin for MRSA (resistance can develop relatively easily if used alone).

## LEGEND for TABLE

### High.

These are essential antibiotics for treatment of human infections where there are few or no alternatives for many infections. Also have been called “critical”, “last-resort” or “last line” antibiotics.

### Med = Medium.

There are other alternatives available but less than for those classified as Low;

### Low.

There are a reasonable number of alternative agents in different classes available to treat most infections even if antibiotic resistance develops

*Adapted from Table 7.2 JETACAR 1999*