

FDA (USA) Guideline document on classification of antibiotics used in veterinary medicine (food animals)

“Take home” messages

- The growing threat to human health posed by microorganisms becoming resistant to antibiotics has been highlighted by many organisations in the human health field e.g. WHO and many National Governments across the world.
- The Food and Drug Administration (FDA) in USA have recognised that there are several important sources for this problem including inappropriate use of antibiotics in humans.
- In UK an expert human/veterinary microbiological advisory group to the Government has stated that “given the available evidence treatment failure in human medicine is more likely to arise from sub-optimal antimicrobial use in humans”.
- Whilst in the case of highly significant human diseases such as multi-resistant tuberculosis the use of antibiotics in animals has no relationship to the problem, in others, such as certain foodborne diseases, the use in animals of certain antibiotics may have a role in the causation of antibiotic resistance in man.
- As a regulatory tool authorities such as FDA have begun a process of categorizing antibiotics according to their significance in human medicine.
- The most important antibiotics, “Critically important”, have been identified as:
 - Fluoroquinolones
 - Macrolids e.g. erythromycin
 - 3rd generation cephalosporins
 - Trimethoprim-sulfas.
- The pleuromutilins (Tiamulin, Valnemulin) are not included on FDA’s List in any category, unlike tylosin, tilmicosin (macrolids) and lincomycin (lincosamide like clindamycin). This exclusion is presumably on account of the fact that the pleuromutilins are not used in human medicine.

...unlike tylosin, tilmicosin (macrolids) and lincomycin (lincosamides like clindamycin), pleuromutilins are not used in human medicine

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In December 1999 the FDA announced that it would consider as an additional regulatory issue the question of the possible increase of resistance to antibiotics in bacteria resident in food animals. This resistance is considered to arise following the use in food animals of certain antibiotics.

In December 2000 they issued their so called “Framework Document” which described for the first time FDA’s plan to use “risk assessments” of the development of antimicrobial resistance, when determining the human safety of antimicrobials administered to food producing animals. In September 2002 a draft guidance document was published and put out for comment to Industry and other interested parties.

The final guidance document now released is presented to assist companies to provide appropriate data to FDA.

The information is required to demonstrate that an antibiotic can be used to medicate food producing animals without encouraging the development of resistant bacteria in the medicated animals, which could create a threat to public health.

The key to the guidance is a “qualitative risk assessment”. The Animal Health Company sponsoring a candidate antibiotic will be required to determine:

1. The probability of the antibiotic fostering the development of resistant bacteria in the animals being medicated (release assessment).
2. What is the possibility of humans ingesting the resistant bacteria (exposure estimate).
3. What is the possibility that the ingestion of the resistant bacteria will result in human health concerns (consequence assessment).

Each of the above three steps would be assigned a score of:

- “Low” risk
 - “Medium” risk
- or “High” risk.

For example, if an antibiotic used in food animals was shown to be likely:

- a) to foster the development of resistant bacteria in medicated animals
- b) that humans were likely to ingest the resistant bacteria
- c) that the ingested bacteria were likely to cause an infection in man, which would result in human health concerns

...then the antibiotic would be given a “high” risk score. In these circumstances the FDA could take a range of “risk management” actions, e.g. denying approval or an approval incorporating stringent restrictions on conditions of use.

An essential component of part 3, “the consequence assessment”, is a process of ranking of antibiotics for use in food animals according to their importance in human medicine.

This ranking process is likely to be of crucial importance to animal health companies in the future. In the EU the advisory committee on veterinary medicines to the European Medicines Evaluation Agency (EMA), known as CVMP, stated in July 1999 that:

“ all antibiotics used in veterinary medicine **except for pleuromutilins** are related to or identical to human medicinal products and can select for cross-resistance or co-resistance”

In the UK the Veterinary Products Committee, which advises the Veterinary Medicines Directorate, (in much the same manner as the CVMP advises the EMA at EU level) recommended in 2001 that:

1. Antibiotics essential for the treatment of a serious or life threatening disease in humans for which there is no alternative, or
2. where the antibiotic is a member of a class that may cause cross-resistance to antibiotics essential for human therapy

...should only be authorised for use in animals with special consideration by the licensing authorities. These recommendations have now been fully endorsed by the UK Government (Vet. Record. November 8th 2003 p575).

The FDA in USA have also now produced a list of antibiotics which have been classified as:

“Critically” important
“Highly” important
or “Important”

...to human medicinal therapy.

The pleuromutilin antibiotics are not included in the list, presumably since no members of the pleuromutilin family are used in human medicine.

However many antibiotics which currently have important uses in veterinary medicine are characterized as being of “critical” importance in human medicine, e.g. fluoroquinolones, macrolids, 3rd generation cephalosporins and trimethoprim-sulfas.

The FDA have defined five factors (factor 1 being the most significant) to rank the importance of an antibiotic in human medicine.

1. Used to treat enteric pathogens which cause foodborne disease.
2. Sole therapy or one of few alternatives to treat serious human disease or antibiotic is an essential component among many antibiotics in the treatment of human disease, e.g. vancomycin or linezolid for methicillin resistant staph. aureus infections (MRSA) or polymyxin for multi-antibiotic resistant *Pseudomonas aeruginosa* infections.
3. Antibiotics used to treat enteric pathogens in non-foodborne diseases.
4. No cross-resistance within antibiotic class and absence of linked resistance with other antibiotic classes.
5. Difficulty in transmitting resistance elements within or across genera and species of organisms. i.e. antibiotics whose resistance mechanisms rely on plasmids and transposons would be less valuable than those whose resistance mechanism was chromosomal.

Thus:

“Critically important” antibiotics must meet criteria 1 & 2 above

“Highly Important” antibiotics must meet either criteria 1 or 2

“Important” antibiotics must meet either criteria 3 and/or 4 and/or 5.

On this basis the following classifications have been made by FDA.

“Critically Important” antibiotics in human medicine

- Fluoroquinolones
 - Macrolids e.g. erythromycin
 - 3rd generation cephalosporins
 - Trimethoprim-sulfa combination's
-

“Highly” Important antibiotics in human medicine

- Natural penicillins
 - Penicillinase resistant penicillins
 - Antipseudomonal penicillins
 - Aminopenicillins
 - 4th generation cephalosporins
 - Carbapenems
 - Aminoglycosides
 - Clindamycin (belongs to group of lincosamides)
 - Tetracyclines
 - Glycopeptides
 - Streptogramins e.g. dalfopristin/quinupristin
 - Oxazolidones
 - Pyrazinamide
 - Isoniazid
 - Rifamycins
 - Chloramphenicol
 - Metronidazole
 - Polymyxin B.
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“Important antibiotics” in human medicine

- 1st generation cephalosporins
 - 2nd generation cephalosporins
 - Cephamycins
 - Monobactams
 - Quinolones
-



Dr Ulrich Klein
International Technical Services
Manager, Pig Products



Dr David Miller
Demafarma Consultancy Ltd

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