



Antimicrobials for veterinary use – regulatory aspects

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Committee of Medicinal Products for Veterinary Use (**CVMP**)


- grants marketing authorisations (centralised procedure)
- provides guidance documents
- handles referrals from Member States

Scientific Advisory Group on Antimicrobials (**SAGAM**) provides scientific input

Demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

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- A vertical blue bar with five yellow stars, positioned to the left of the list of requirements.
- The mechanism of action should be reported including spectrum of activity
 - MIC-values should be from different areas and epidemiologically unrelated
 - A PK/PD-analysis should be carried out
 - Resistance mechanisms should be described
 - Dose confirmation and field studies should be conducted using bacteriological and clinical endpoints

Summary of Product Characteristics


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- A vertical blue bar with five yellow stars, positioned to the left of the list.
- A part of the approval
 - Defines the indication and posology
 - Adds warnings, precautions and contraindications
 - The base for all marketing
 - Available on websites (www.emea.europa.eu or national)
 - Also assessment report (EPARs) are available

Guideline on the SPC for antimicrobial products


- The target bacterial species should be listed and the indications detailed
- Prudent use warnings should be given
- Wild type MIC:s should be presented
- Clinical breakpoints should be presented with their references
- Epidemiological cut-off values used be used to characterise isolates of food-borne bacteria



VICH GL36

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- A vertical blue bar on the left side of the slide, containing five yellow stars arranged vertically, similar to the European Union flag.
- General approach to establish a microbiological ADI
 - Are residues active against bacteria in the human gut flora? Will they enter the human colon, still being active?
 - Endpoints: Disruption of the colonization barrier and increase in the population(s) of resistant bacteria in the human colon
 - Method dependent...

VICH GL27

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- A vertical blue bar with five yellow stars, positioned to the left of the list items.
- Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance
 - Characterise the potential for the use of the product to select for antimicrobial-resistant bacteria of human health concern
 - Mapping of resistance mechanisms and exposure to pathogens and commensal organisms

Post-marketing authorisation measures and pharmacovigilance

- Monitoring of antimicrobial resistance in zoonotic and commensal bacteria
- Sufficient data quality
- Both companion and food producing animals
- Complementary to public monitoring programs
- Lack of efficacy is seldom reported




Public statement on the use of (fluoro)quinolones in food producing animals in the European union: Development of resistance and impact on human and animal health

- FQs should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials (to be considered prior to approval as a part of the developmental plan)
- Warnings included for existing products






- The dosage regimens of FQs should be carefully determined to ensure optimal efficacy and reduce selection of resistance
- Plasmid mediated FQ resistance complicates the picture
- Group and flock medication is currently under discussion

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Reflection paper on the use of 3rd and 4th generation cephalosporins in food-producing animals in the European union: Development of resistance and impact on human and animal health

- Systemic broad spectrum cephalosporins should be reserved...
- Use of systemic cephalosporins for groups or flocks of animals should be discouraged
- Prophylactic use should be reserved for specific circumstances

SAGAM Workplan 2008


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- A vertical blue bar on the left side of the slide, containing five yellow stars arranged vertically, similar to the flag of the European Union.
- Initiate corresponding work on macrolides to cover the third group of critically important antimicrobials for humans
 - Focus on MRSA
 - Continued work on FQs with focus on dosing in case of group and flock medication

Clinical trials and prudent use guidance

- Study population should be representative for the target population
- Problematic when sponsors chose inappropriate study populations




“The cascade”

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Where there is no authorized medicinal product for a condition, by way of exception, the veterinarian responsible may, under his/her direct personal responsibility and in particular to avoid causing unacceptable suffering treat the animals concerned...

In practice...

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- A vertical blue bar with five yellow stars, similar to the European Union flag, positioned on the left side of the slide.
- Different prescription pattern and compliance due to e.g. different traditions
 - E.g. in BE, out of 50 randomly chosen farms 88 % used group treatment*
 - The incidence varied from 0 to 1400 daily doses /1000 pigs*
 - Oral treatment was generally underdosed whereas injectables were overdosed*
 - < 1 % use of FQs or 3G-cephs for group treatment*

*Timmerman *et al* (2006) Preventive Veterinary Medicine 74:251–263

Prophylaxis

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- A vertical blue bar on the left side of the slide, containing five yellow stars arranged vertically.
- The need of prophylactic use should be reserved for specific circumstances
 - The presence of the disease in the herd should be established before preventative treatment (Draxxin, Econor)
 - The prevention strategy should include efforts to eliminate the infection from the parent generation (Aivlosin, chicken)
 - There are production forms that are more dependent on prophylaxis than others


Prophylaxis cont.

- Reduced susceptibility to cefotaxime in *E coli* was detected in farms where ceftiofur was used (5/10 farms vs 1/10 controls)**
- In 8/10 farms ceftiofur was used for systematic prophylaxis in 1-day-old piglets**

** Jørgensen *et al* (2007) Journal of Antimicrobial Chemotherapy; 50:1040-2




Abuse of the cascade


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- A vertical blue bar on the left side of the slide, containing five yellow stars arranged vertically.
- Evidence based medicine might not always be prudent use
 - Bactroban (mupirocin) is reserved for eradication of MRSA colonisation - no approved veterinary indication (SE recommendations)
 - But this is evidence based medicine*
 - The newer might not be the better!

* Small Animal Dermatology, 6th ed, Scott, Miller, Griffin sid 279-280

But cascade use might be prudent...

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- A vertical blue bar with five yellow stars arranged vertically, positioned to the left of the list items.
- Lack of products with “old molecules”
 - Old products have less budget for product development
 - Administration form important factor in vet med

Money, education and prudent use...

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- A vertical blue bar with five yellow stars, positioned to the left of the list items.
- Biosecurity might be more expensive than antimicrobials
 - Veterinarians might not show interest in strategies to minimise antimicrobial resistance
 - Veterinarians' income might be dependent on antimicrobial sales volumes
 - A global approach and a clear message is needed

CVMP strategy on antimicrobials 2006-2010 and status report on activities on antimicrobials

- Ensure availability of antimicrobial products for veterinary use so that the use of these products is efficient, whilst safeguarding against the development of resistance
- Focus on prudent use instructions
- Work for enhanced communication and an open dialogue

Is there a link between veterinary use of antimicrobials and occurrence of MRSA?

- In general – there is always a risk for resistance when antimicrobials are used
- What is the link between herd management (including antimicrobial use) and presence of MRSA?
- How much does vet use contribute to the overall selection pressure (including human medicine)?
- Are there any measures related to vet use of antimicrobials to be taken urgently?

We need collaboration to find the answers

- Biosecurity and prudent use remain crucial
- A global approach is needed
- Many different stakeholders at different levels (such as regulators, risk assessors, academia, vet practitioners, producers and consumers) need to be involved

