Use and regulation of antimicrobial agents for animals

Seminar on Antimicrobial Resistance and the veterinary and food sector
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Use of antimicrobials in the European Union

- All market authorizations as growth promoters withdrawn 31.12.2006
- Strict regulations for Marketing Authorisations of antimicrobials
- Stricter regulations for fluoroquinolones, cephalosporins and macrolides
- Antimicrobials for food producing species need to have a Maximum Residue Limit established before can be authorised
- Prescription only products
Committee for Medicinal Products for Veterinary Use (CVMP) strategy on antimicrobials 2011-2015*

- Responsible use of antimicrobials is regarded a cornerstone to contain resistance for benefit of both animal and human health.
- CVMP to work with other interested parties to promote responsible use of antimicrobials.
- Responsible use principles need to be implemented in everyday life at farms and animal clinics.


CVMP guidance on antimicrobials

- General approach to establish a microbiological ADI (VICH GL36)
- Preauthorisation requirements for authorisation of antimicrobials – potential to select for resistance (VICH GL27)
- Summary of Product Characteristics (SPC) of antimicrobials (revised)– prudent use
- Demonstration of efficacy for antimicrobials
- Reflection Paper on Antimicrobial Resistance Surveillance as Post-Marketing Authorisation Commitment

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Maximum Residue Limits and antimicrobials

Revised VICH GL36: Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI

- Disruption of the colonization barrier
- Increase in the population(s) of resistant bacteria in the human colon
- Detection of changes in the population of resistant bacteria
- Derivation of a microbiological ADI
- Potential effects on the microorganisms used for industrial food processing

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VICH GL27 (pre-authorisation)

Applicable in E.U., Japan and the U.S.

1. Basic information
   1.1 Antimicrobial class
   1.2 Mechanism and type of antimicrobial action
   1.3 Antimicrobial spectrum of activity
   1.4 Antimicrobial resistance mechanisms and genetics
   1.5 Occurrence and rate of transfer of antimicrobial resistance genes
   1.6 Cross-resistance and 1.7 Co-resistance
   1.8 Pharmacokinetic data

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2. Additional information
   2.1 *In vitro* mutation frequency studies
   2.2 Antimicrobial agent activity in intestinal tract
   2.3 Other animal studies
   2.4 Supporting information

3. Discussion

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3rd and 4th generation cephalosporins

“Product name (XXX)” selects for resistant strains such as bacteria carrying extended spectrum betalactamases (ESBL) and may constitute a risk to human health if these strains disseminate to humans e.g. via food. For this reason, “XXX” should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly (refers to very acute cases when treatment must be initiated without bacteriological diagnosis) to first line treatment.”

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3rd and 4th generation cephalosporins referral

- All references to poultry to be deleted from SPC. A warning is added:

“Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.”


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Quinolones, including fluoroquinolones*

“Official and local antimicrobial policies should be taken into account when the product is used.”

“Whenever possible, fluoroquinolones should only be used based on susceptibility testing.”

“Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other (fluoro)quinolones due to the potential for cross resistance.”


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Fluoroquinolones

“Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.”

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Macrolides, lincosamides and streptogramins* - recommendations

- Prudent use of antimicrobials should be strongly promoted.
- Macrolides are a first line treatment against a number of animal diseases.
- Need to avoid overuse, for e.g. general prophylaxis where no specific diagnose is evident or where the disease in question would self cure without antimicrobials.


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European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)

- The ESVAC collects data on sales of antimicrobials to animals.
- A report is produced annually.
- A population correction unit (PCU) used as a proxy for the animal biomass of food producing species at risk for being treated in the country of question.
- Takes into account transport of animals to another MS for fattening or slaughther

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Countries participating in ESVAC 2010*

ESVAC 1st report: 8 EU/EEA countries provided data aggregated by class
ESVAC 2nd report: 19 EU/EEA countries provided data according to the ESVAC template.

*Italy provided data for 2010. Will be included in 2011 report

Countries participating in ESVAC 2011

ESVAC 3rd report: 26 EU/EEA countries have provided data according to the ESVAC template.
ESVAC 2010 report - disclaimer

- It is generally agreed that it takes at least 3 to 4 years in order to establish a valid baseline for the data on sales of veterinary antimicrobial agents.
- Data presented in this report should not be used alone as a basis for setting management priorities, but should always be considered together with data from other sources.

Results cont.

Sales of veterinary antimicrobial agents in 2010 in 19 countries by form, in mg/PCU
Results cont.

Sales in 2010 of veterinary antimicrobial agents for individual treatment and for herd treatment in 19 countries, in mg/PCU

- 84% for individual treatment
- 16% for herd treatment

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Results cont.

Sales for food producing species, including horses, in mg/PCU, of the various veterinary antimicrobial classes in 2010 by country

1 Differences between countries can partly be explained by differences in animal demographics, in the selection of antimicrobial agents and in dosage regimes, among other factors
Results cont.

Percentage of sales of the most-selling veterinary antimicrobial agents, in mg/PCU, of total sales aggregated by 19 countries in 2010

- Tetracyclines: 39%
- Penicillins: 23%
- Sulfonamides: 11%

Results cont.

Sales of macrolides, fluoroquinolones and 3rd- and 4th-generation cephalosporins, in % of total sales, for food-producing species, including horses, in mg/PCU, by country, for 2010
ESVAC summary

- The major part of the sales of veterinary antimicrobial agents in the 19 countries is for herd treatment but considerable variations between countries.

- The prescribing patterns of the various antimicrobial classes, expressed as mg/PCU, varied substantially between the countries.

ESVAC summary cont.

- Of total sales tetracyclines, penicillins and sulfonamides are the most-selling veterinary antimicrobial agents, both by country (range 61-81%) and overall (73%) in the 19 countries.

- Overall in the 19 countries the sales, in mg/PCU of the most CIAs account for 8% of total sales.

- The percentage of sales of the most important CIAs varies considerably between countries (range 0.2%-12%).
Summary cont.

• An apparent 30-fold difference in the sales, expressed as mg/PCU, is observed between the most- and least-selling countries.

• This is in part likely to be due to
  – differences in the composition of the animal population in the various countries
  – variation in terms of dosage used, length of treatment period or formulation of the various antimicrobial agents used;

• However, these factors can only partly explain the differences; other factors also need to be considered.

The future – data per species and units of measurement

ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals
Latest CVMP publications on antimicrobials

Antimicrobial resistance risk assessment concept paper. Out for consultation until 30 April 2013

Use of pleuromutilins in food-producing animals in the EU: Out for consultation until 30 Jun 2013

Usage of veterinary therapeutic antimicrobials in Denmark, Norway and Sweden following termination of antimicrobial growth promoter use. Preventive veterinary medicine 75:123-132.

Fig. 1. Annual sales in Denmark, in tons active substance, of antimicrobial growth promoters (AGPs) and of veterinary antimicrobials for therapeutic use (antimicrobials for use in farmed fish not included). Data on sales of AGPs were collected from the Danish Plant Directorate (from 2001 by VetStat); sales data for veterinary antimicrobials are estimated based on sales from pharmaceutical industry to pharmacies and from feed mills to farmers while from VetStat. Data for 1995 not included because they were not assumed to be useful (AVO = avoparcin).

CVMP recommendations on responsible use

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Fig. 3. Annual sales in Norway, in tons active substance, of antimicrobial growth promoters (AGPs) and of veterinary antimicrobials for therapeutic use (antimicrobials for use in farmed fish not included). Data on sales

Fig. 5. Annual sales in Sweden, in tons active substance, of antimicrobial growth promoters (AGPs) and of veterinary antimicrobials for therapeutic use in Sweden (antimicrobials for use in farmed fish not included). Data for the years 1985, 1987 and 1989 are missing. Data on usage of AGPs were collected from Swedish Board of Agriculture; data on sales on veterinary antimicrobials were collected from Apoteket AB, Sweden.