Focus Group Meeting on Fluoroquinolones:

Introductory remarks
– Use of Fluoroquinolones in Europe

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PLAN

• INTERNATIONAL DEVELOPMENTS
• EU/ CVMP ACTIONS
• R/B FLUOROQUINOLONES
• EXPOSURE
  – Use of Fluoroquinolones in Europe
• RECOMMENDATIONS
International developments

- March 2004 FAO/WHO/OIE consultation in Oslo, Norway
- FDA 2005 withdrawal of approval of the new animal drug application for enrofloxacin in poultry,
- February 2005 Canberra, Australia - CIA for Human medicine
- May 2006 OIE International Committee Resolution N° XXXIII - preliminary list of antimicrobials of veterinary importance
- June 2006 Codex Task Force on Antimicrobial Resistance to be established
- October 2006 Meeting of OIE ad hoc group on antimicrobial resistance
CVMP ACTIONS

- EMEA/CVMP/818/99 A Risk Management Strategic Plan for controlling Antimicrobial Resistance through the Authorisation of Veterinary Medicines
- EMEA/V/2379/99 EMEA Risk Assessment on Antimicrobial Resistance in Veterinary Medicine
- EMEA/CVMP/342/99 Antibiotic Resistance in the EU associated with Therapeutic Use of Veterinary Medicines - Report and Qualitative Risk Assessment by the CVMP.
- EMEA/CVMP/627/01 Revised Guideline on Antimicrobials for general Veterinary Use in Target Animal Species
- EMEA/CVMP/612/01 Guideline on the SPC for antimicrobial products
- EMEA/CVMP/244/01 Guideline on Pre-authorisation Studies to assess the Potential for Resistance Resulting from the Use of Antimicrobial Veterinary Medicinal Products (superseded by: VICH Topic GL 27 (CVMP/VICH/644/01) Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to Antimicrobial resistance
- EMEA/CVMP/699/04 CVMP Scientific Advisory Group on Antimicrobials
- EMEA/V/3783/04 CVMP comments to the Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance, Scientific Assessment in preparation of the 2nd Workshop on Management Options
CVMP POLICY

- EMEA/CVMP/353297/05 CVMP Strategy on Antimicrobials 2006-2010 and Status Report on Activities on Antimicrobials
  - Focus on prudent use (ongoing revision of Guideline on the SPC for antimicrobial products)
  - Fluoroquinolones and cephalosporines

Benefits of FUOROQUINOLONES

For animals: FQs are efficient and valuable antimicrobials. For some serious animal indications, FQs are the only alternative available.
Risk Assessment

Codex definition: A scientifically based process consisting of the following steps:

• (i) hazard identification,
• (ii) hazard characterization,
• (iii) exposure assessment, and
• (iv) risk characterization.
HAZARD IDENTIFICATION

• Use of antimicrobials conduct to selection of resistant bacteria
HAZARD CHARACTERISATION

IN ANIMALS:

• Use of (F)Qs in animals → resistance in animal pathogens and food-borne zoonotic pathogens → negative effects on treatment of infections with these organisms in animals and humans

• If (F)Qs lose their activity or are no longer available for the treatment of animal diseases → antimicrobial therapy of some diseases will be complicated → animal welfare and public health concerns → economical losses.
HAZARD CHARACTERISATION

IN HUMANS

- **FQs** = critically important antimicrobials for severe and invasive infections
  These infections are predominantly caused by organisms unrelated to animals
  - uncomplicated acute gastroenteritis (Salmonella or Campylobacter): antibiotics are not indicated or even contra-indicated in some countries
  - complicated Salmonella infections: FQs are important
    resistance to (F)Qs affects the therapeutic options
    alternative antibiotics exist
  - complicated Campylobacter infections: macrolides (erythromycin, azithromycin) are considered the drugs of choice.
- Nalidixic acid resistant S. Typhimurium infections
  increased risk of hospitalisation and mortality
  FQ and macrolide resistant Campylobacter infections
  increased risk of hospitalisation and complications
EXPOSURE ASSESSMENT

Comparison Animal/Human Use in FRANCE

**Quinolones**
- **HUMANS**: 20.05% (4.3 T)
- **ANIMALS**: 79.95% (17.15 T)

**Fluoroquinolones**
- **HUMANS**: 89.17% (34.8 T)
- **ANIMALS**: 10.83% (4.14 T)

**TOTAL**
- **HUMANS**: 39.1 T
- **ANIMALS**: 21.3 T
### Sales of fluoroquinolones and quinolones (tonnes active substance) and production of meat in some Member States

<table>
<thead>
<tr>
<th>Country</th>
<th>Sales of antimicrobials (metric tonnes)</th>
<th>Production of meat (metric tonnes slaughtered)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>All quinolones</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Finland</td>
<td>&lt; 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>France</td>
<td>3.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20.7</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Portugal</td>
<td>3.6</td>
<td>no information</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.2</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>no information</td>
</tr>
</tbody>
</table>

- <sup>b</sup> Includes dogs and cats
- <sup>c</sup> Broilers only

**Harmonisation of data collection on the use of antimicrobial agents needed**
CVMP reflection paper on
the use of FQs in food-producing animals

441 Products

Number of (fluoro)quinolones per Country

European Medicines Agency (EMEA), London, UK

www.emea.eu.int
CVMP reflection paper on the use of FQs in food-producing animals

Quinolones authorised in the EU for food-producing animals as veterinary medicinal products:

- Oxolinic acid
- Flumequine
- Danofloxacin
- Difloxacin
- Enrofloxacin
- Marbofloxacin
- Sarafloxacin
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Total number of (fluoro)quinolones in 23 European Countries

- Danofloxacin: 27
- Difloxacin: 23
- Enrofloxacin: 222
- Flumequine: 88
- Marbofloxacin: 37
- Oxolinic acid: 40
- Sarafloxacin: 2

European Medicines Agency (EMEA), London, UK
www.emea.eu.int
CVMP reflection paper on the use of FQs in food-producing animals

Number of (fluoro)quinolone MA per pharmaceutical form

- Danofloxacin
- Difloxacin
- Enrofloxacin
- Flumequine
- Marbofloxacin
- Oxolinic acid
- Sarafloxacin

Marketing Authorisations

- Injectable
- Powder/liquid solution
- Premix
- Bolus
- Bolus
- Other
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Number of (fluoro)quinolones per species

- **Bovine**: Danofloxacin (89), Difloxacin (32), Enrofloxacin (34), Flumequine (7), Marbofloxacin (9), Oxolinic acid (2), Sarafloxacin (10)
- **Pigs**: Danofloxacin (20), Difloxacin (7), Enrofloxacin (10), Flumequine (9), Marbofloxacin (2), Oxolinic acid (6), Sarafloxacin (0)
- **Ovine**: Danofloxacin (89), Difloxacin (0), Enrofloxacin (0), Flumequine (0), Marbofloxacin (0), Oxolinic acid (0), Sarafloxacin (0)
- **Poultry**: Danofloxacin (63), Difloxacin (57), Enrofloxacin (18), Flumequine (4), Marbofloxacin (2), Oxolinic acid (1), Sarafloxacin (1)
- **Fish**: Danofloxacin (9), Difloxacin (4), Enrofloxacin (0), Flumequine (0), Marbofloxacin (0), Oxolinic acid (0), Sarafloxacin (0)
- **Other**: Danofloxacin (10), Difloxacin (18), Enrofloxacin (0), Flumequine (0), Marbofloxacin (0), Oxolinic acid (0), Sarafloxacin (0)
CVMP reflection paper on the use of FQs in food-producing animals

Repartition between Species in France

- **poultry**: 1,58T (37%)
- **bovine**: 1,14T (26%)
- **porcine**: 1,25T (29%)
- **cats**: 0,02T (0%)
- **dogs**: 0,34T (8%)
RISK CHARACTERISATION

- No quantitative risk has been performed
- Potential Risk
- Management measures to be implemented
• Actions to maintain the efficacy of fluoroquinolones for veterinary use are needed
• 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
• Dosage regimens of FQs should be carefully determined on the basis of PK/PD properties
• Prudent use instructions should be included in all antimicrobial products SPCs and literature
"Take one capsule tonight, and if there’s no improvement by tomorrow morning, take the whole bottle."
Thank you!