EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# EMA advice on the impact of the use of antibiotics on public and animal health: Potential impact on the authorisation of antimicrobials

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# Background

- April 2013: EMA received a request from the Commission for advice on the impact of the use of antibiotics on public and animal health
- This advice is part of the EC Action Plan against the rising threat from AMR
- The answers were prepared by the Antimicrobial Advice ad hoc Expert Group “AMEG”
- The AMEG is an interdisciplinary group with experts from: EMA, CVMP, AWP, IDWP, EFSA, ECDC, JIACRA
- Input was also received for Qs 3. & 4. at a stakeholder meeting (Feb 14) and during two public consultations

## **Q.1**: Advice on **"old" antibiotics**, or **new** antibiotics belonging to **old classes**, now **re-introduced into human medicine** to treat MDR infections

To answer this Q., AMEG undertook a risk profiling for:

- **Tigecycline**, a glycylcycline – new antimicrobial derived from an old class (Tetracyclines); not authorised for use in vet medicine

- **Colistin**, an "old" antimicrobial which has been used for decades in vet medicine

# Tigecycline (TIG)

- **Last resort therapy** for treatment of complicated soft tissue and abdominal infections in humans
- Use of TIG under Cascade reported in dogs and cats to treat MRSA/P – extent unknown

*AMEG conclusions*

- Veterinary authorisation could lead to rapid development of TIG-R in zoonotic bacteria (Enterobacteriaceae, *Acinetobacter*)
- The risk of transfer of resistance from animals to humans would have to be considered in a **full AMR risk assessment** for any future VMP
- Currently appears to be limited need for TIG in vet medicine and **unlikely that a positive benefit-risk** could be established for a MA

# Colistin

- **Last resort therapy** for infections in humans due to various MDR infections (esp. carbapenem-R bacteria)
- Used for decades in vet medicine as group treatment for **gastrointestinal infections in livestock**
- **Low levels of resistance** in livestock bacteria; COL-R unstable and slow to spread

*AMEG recommendations*

- Maintain use of Colistin in vet med due to its **therapeutic importance**
- **SPC** indications and warnings **revised in line with responsible use** – CVMP Art. 35 referral
- **Surveillance**: of use and bacterial susceptibility using standardised testing

# **Q.2**: A **Categorisation** of the WHO critically important antimicrobials (**CIAs**) based on their degree of risk to man due to AMR development following use in animals

Factors considered in the AMEG Categorisation:

CIAs **authorised** for use in vet medicine were categorised according to

- The **need** for the antimicrobial **in human medicine**: sole therapy or few alternatives
- **Probability of resistance transfer** from animals to humans (mechanisms of resistance, food-borne transmission)

CIAs **not authorised** for use in veterinary medicine

# The three categories

## Authorised CIAs

**Category 1: Low / limited risk** to public health

- narrow spectrum Penicillins, Macrolides, Tetracyclines, Polymixins
- General principles of responsible use to be applied

**Category 2: Higher risk** to public health

- Fluoroquinolones, systemic 3/4G Cephalosporins, (Aminoglycosides, broad-spectrum Penicillins)
- Restricted to use where there are no alternatives or response to alternatives expected to be poor

**Category 3: CIAs** currently **not authorised** for use in vet medicine

- Currently restricted to Cascade use in companion animals only
- Use to be kept to a minimum for Carbapenems, Monobactans, etc

*Further AMEG comments:*

The Categorisation is **only one element** to consider when assessing the risk to public health of use of a **VMP**:

- AMR risk will differ according to **species, route of administration, dose regimen**, etc
- For treatment guidelines, **local AMR situation** and product availability have to be considered
  - **Animal welfare** and disease severity should be taken into account

# **Q.3**: Advice on the impact on public health of authorising **new classes** of antimicrobials for veterinary use, and whether there is a need to **restrict or ban** the use of certain new classes

Stakeholders provided examples of indications for which they consider there is currently a lack of antimicrobial VMPs:

- Coliform infections, colibacillosis, neonatal diarrhoea, sepsis, mastitis
- *Brachyspira hyodysenteriae* in pigs
- *Rhodococcus equi*,
- Enterococci and respiratory Mycoplasma in poultry
- Bovine respiratory disease and bovine interdigital dermatitis
- ESBL *E coli*; MRSA, MRSP in companion animals
- (Minor species)

AMEG considered that general conclusions cannot be drawn on the risk to public health of the authorisation of new antimicrobial VMPs, but known risk factors can be taken into account.

*AMEG Recommendations*

- A **risk assessment** (RA) is needed for each new antimicrobial to address its **importance to human health** and the **risk for AMR transfer** from animals
- For a **VMP** authorisation, the **full RA** should take into account the **conditions of use** of the VMP (species, route, dose, etc)
- Authorisation depends on a **positive benefit-risk for the VMP**
- **Approved programmes** should be in place to monitor evolution of **susceptibility** in zoonotic/commensal bacteria

*Further AMEG recommendation*:

- Introduce an **early hazard analysis** for new antimicrobial substances to consider the **importance of the AM to human medicine** and identify **"drug-bug-AMR" hazards** of zoonotic relevance. This could:
  - Forewarn applicants of the need for **risk management measures** to be applied for any future VMP
  - Allow consideration of restrictions on **Cascade use**

## **Q.4**: Advice on **Risk Management Options** (RMO) for human CIAs that are **currently authorised** for use in veterinary medicine

Stakeholders were asked to provide examples of:

- RMO that have already been applied and their outcomes
- The possible need for future RMO
- The impact of the expiry of marketing exclusivity on sales and usage patterns of CIAs

- AMEG provided a review of risk management measures that have been implemented in various EU member states.

- Concluded that **evaluation of their effectiveness is complex**: difficult to link veterinary use with AMR in man; often several measures are implemented simultaneously; co-resistance, etc.

- Also have to **consider potential negative effects on animal welfare** that may result from restrictions

## *AMEG recommendations for **Risk Management Options** for **currently authorised CIAs***

- There are already a number of recommendations in place from OIE, EFSA and CVMP, e.g. **CVMP's recommendations on the use of 3/4G Cephalosporins, Fluoroquinolones**, etc.

- Further risk profiling should be undertaken for certain **broad-spectrum penicillins** and **aminoglycosides**

- **RMO** should be based on a **dedicated risk assessment**

Regulatory RMO can be considered within the **benefit-risk assessment** and **SPC**/authorisation of a product:

- Restriction from prophylactic or metaphylactic use
- Restrictions on route of administration (e.g. group treatments via food/water)
- Application of responsible use warnings to SPC
- Restrictions on Cascade use
- Requirement for post-authorisation surveillance (sales, use)
- Marketing of pack-sizes according to posology
- Withdrawal/suspension of MA after risk assessment shows benefit-risk is no longer positive

**Generic products**: increased availability and the competitive economic environment that result after generic products enter the market may increase the consumption of an antimicrobial substance.

Together with evolution of bacterial susceptibility since first approval, this increased exposure could alter the AMR risk.

*AMEG recommendation*

- Based on the **outcome of usage and AMR surveillance** post-authorisation, a **new AMR risk assessment** could be required for all VMPs of a specific class including **both generic and reference products**.

# General conclusions in regards to **potential** impact of AMEG advice on the authorisation of antimicrobial VMPs

- A risk assessment is needed for each new AM to assess its importance to human health and the risk of AMR transfer from animals to humans
- The AMEG has provided a contemporaneous Categorisation that considers these aspects
- For a VMP authorisation, the AMR risk assessment should also take into account the conditions of use of the VMP (species, route of admin etc)
- Risk management options should be based on the tailored risk assessment
- VMP authorisation should be dependent on a positive benefit-risk assessment
- An early hazard identification/characterisation is suggested, possibly prior to MA application to consider if restrictions may apply
- SPC indications and warnings should be in line with principles of responsible use; CVMP recommendations have already been made for certain CIAs
- MAHs should have plans to monitor evolution of microbial susceptibility and there should be surveillance of usage
- Based on the outcome of above, a new RA could be required for all products of a specific AM class (reference products and generics)

# Thanks to....

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## Thank you for listening!

Full Answers to the Commission's request for advice are available on the EMA's website