EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Continue to promote the responsible use of antimicrobials and their alternatives

Underlying actions

EMA's Regulatory Science Strategy to 2025 - Veterinary Stakeholder Workshop

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Comments to the underlying actions represent the views of stakeholders and not the European Medicines Agency.

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Continue to promote the responsible use of antimicrobials and their alternatives 1/2

1. Support prudent and responsible use of antimicrobials, via updated and/or new regulatory guidance and scientific opinion

2. Promote authorisation of alternative approaches to the use of conventional antimicrobials

3. Develop novel regulatory paradigms for efficacy, such as measuring a medicinal product's effect at the level of herd rather than in the individual animal

4. Develop a regulatory approach for bactericidal compounds that are not themselves traditional antibiotics

Continue to promote the responsible use of antimicrobials and their alternatives 2/2

5. Facilitate cooperation between stakeholders in AMR and veterinary vaccine availability

6. Identify funding to generate data, e.g. via modelling and extrapolation, to support existing, including off-patent, antimicrobials

7. Foster development of pen-side and accompanying diagnostics for antimicrobial sensitivity testing

8. Explore linkage of authorisation and use of high-risk antimicrobials with the approval and use of a companion diagnostic

Promote responsible use of antimicrobials and their alternatives – stakeholder comments received

Action 1: Support prudent and responsible use of antimicrobials, via updated and/or new regulatory guidance and scientific opinion

Action 6: Identify funding to generate data, e.g. via modelling and extrapolation, to support existing, including off-patent, antimicrobials

Stakeholder comments:

- *Ensure a One Health perspective*
- *Support given to: optimisation of dosing regimens with use of **PK/PD modelling methods & extrapolation** to maintain availability of established antimicrobials,*
- *and to establish **clinical breakpoints** for AM susceptibility testing*

Promote responsible use of antimicrobials and their alternatives - stakeholder comments received (contd.)

Action 7: Foster development of pen-side and accompanying diagnostics for antimicrobial sensitivity testing

Action 8: Explore linkage of authorisation and use of high-risk antimicrobials with the approval and use of a companion diagnostic.

Stakeholder comment

- *Antibiotic companies or national governments could contribute to development of novel animal/patient side tests to facilitate more accurate choices of medications for specific infections….reducing the chance of treating with an inappropriate medication.*

Promote responsible use of antimicrobials and their alternatives - stakeholder comments received (contd.)

Actions 2, 3 & 4:

- Promote authorisation of alternative approaches to the use of conventional antimicrobials
- Develop novel regulatory paradigms for efficacy, such as measuring a medicinal product's effect at the level of herd rather than in the individual animal
- Develop a regulatory approach for bactericidal compounds that are not themselves traditional antibiotics

Stakeholder comment:

- *Continue to research alternatives. Not only vaccines but also phages, biocides, immunomodulators, essential oils. Essential to find a place in the regulatory context.*

Promote responsible use of antimicrobials and their alternatives

Action 5: Facilitate cooperation between stakeholders in AMR and veterinary vaccine availability

No stakeholder comment received

High level concerns/recommendations raised by stakeholders

Stakeholder comment:

*The goal of **ensuring availability** and **meeting therapeutic challenges** is missing. Ways need to be found to monitor and address gaps in availability.*

Actions identified by the EMA secretariat and session chairs for discussion

- Continued access to established products
- Alternatives to Antibiotics – addressing gaps in the regulatory framework
- What should we be doing at global (OIE, WHO, Codex, TATFAR) level on AM

Continued access to established products

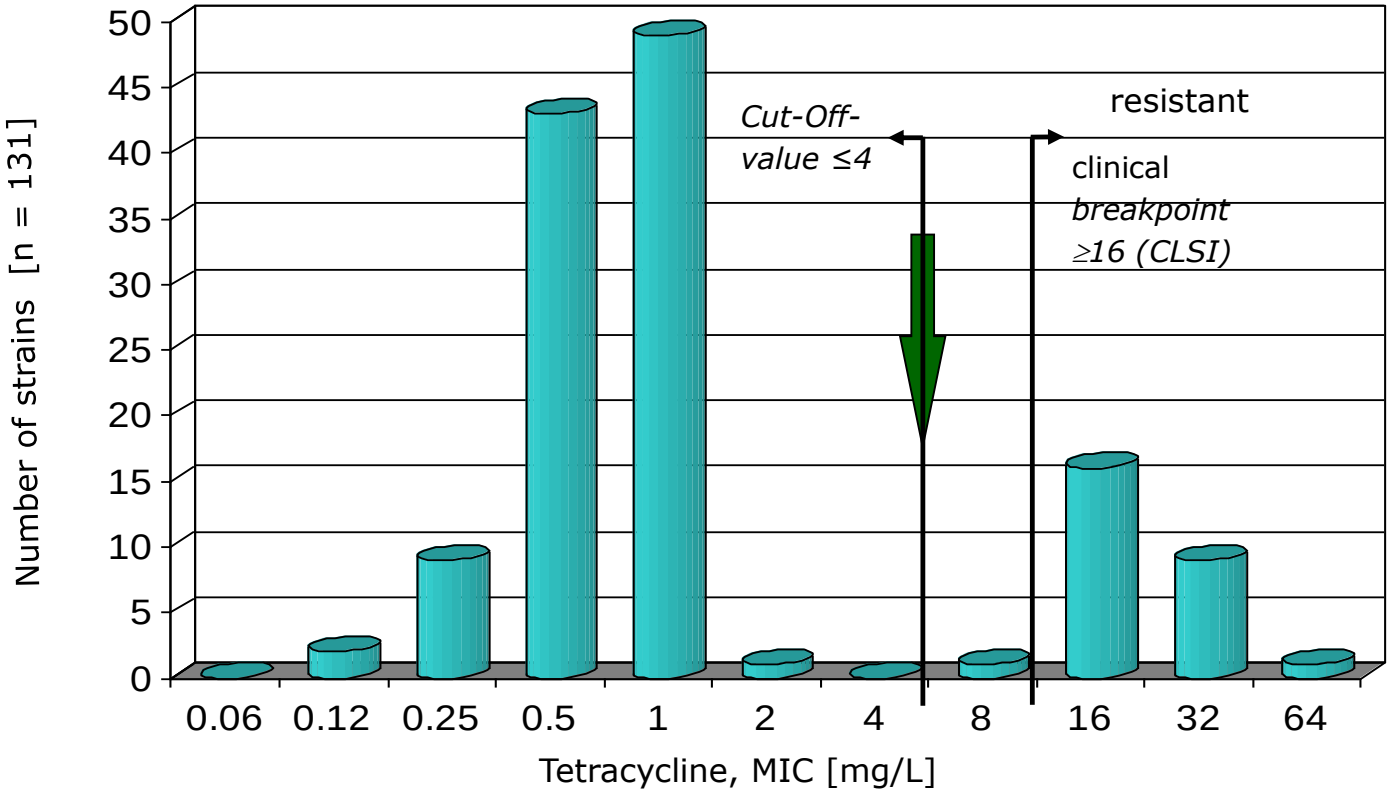
- Use of modelling techniques and data extrapolation for review of dosing regimens - The CVMP's reflection paper on this topic has been out for consultation, and associated SPC harmonisation will be a significant task. Can industry or academia help further with data gaps (in absence of new data protection)?
- One Health approach to the NVR requirements in regard to the Reserved List and Restrictions on Cascade use – What are the potential pitfalls or unforeseen consequences in terms of impacts on public/animal health? E.g. could there be risk for MUMS? How will we harmonise to different practices across EU MSs on use of HMPs and CIAs?
- Use and development of diagnostic tests and clinical break-points to support responsible AMU and detection of AMR – Is this potentially useful? Should this be responsibility of pharma? Should Diagnostic tests be regulated in future by EMA?

Alternatives to antimicrobials – addressing gaps in the regulatory framework

- Clarity on classification of alternative products (e.g. VMPs, feed additives)
- For VMPs: What are acceptable medicinal treatment claims – e.g. reduction in AMU? Stimulation of immunity? How do we design studies to support them?
- Is industry ready to discuss options with EMA? Should we be discussing with international regulatory partners in this area before moving forwards at EU level?
- How to further incentivise the development and authorisation of alternative products? Should those with greatest potential for reducing AMU be identified and prioritised? The CVMP's reflection paper on this topic is out for consultation - stakeholders are encouraged to send comments.

What should we be doing at global (OIE, WHO, Codex, TATFAR) level on AMR?

- Should we be trying to harmonise policy, data collection and analysis?
- What will be the impact of Article 118 (ban on import of animals/ produce treated with AMs on the 'Reserved List')?



***Mannheimia haemolytica*, cattle, 2001/2002**

MIC_{90}: 131 x 0.9 = 117.9 → MIC of 118. isolate: 16 mg/L

MIC_{50}: 131 x 0,5 = 65.5 → MIC of 66. isolate: 1 mg/L

MIC_{90} of *Staphylococcus* spp. isolated from dairy cattle with acute mastitis, Germany 2001

Antimicrobial Agent	*S. aureus* (n=212) MIC_{90}	CNS* (n=192) MIC_{90}
Ampicillin	2	0.5
Amoxicillin/Clav. acid	1/0.5	0.25/0.12
Avilamycin	8	16
Benzyl penicillin	2	0.5
Cephalothin	0.5	0.5
Clindamycin	≤0.12	0.5
Enrofloxacin	0.25	0.5
Erythromycin	0.5	2
Gentamicin	0.5	0.25
Streptomycin	8	8
Tetracycline	1	32
Trimeth./Sulfa.	≤0.12/2.38	0.25/4.75
Vancomycin	1	1

CNS=Coagulase Negative Staphylococcus

MIC_{90} of *P. multocida* isolated from fattening pigs with swine respiratory disease, Germany 2001 and 2002/2003

Antimicrobial Agent	*P. multocida* (n=176) MIC_{90}	*P. multocida* (n=448) MIC_{90}
Ampicillin	0.25	0.5
Amoxicillin/Clav. acid	0.25/0.12	0.25/0.12
Cefquinome	0.12	-
Ceftiofur	0.12	0.06
Cephalothin	0.5	0.5
Enrofloxacin	≤0.03	0.03
Florfenicol	0.5	2
Gentamicin	4	2
Nalidixic acid	8	8
Streptomycin	32	32
Tetracycline	2	2
Trimeth./Sulfa.	4/76	8/152

Deficits in deriving necessary clinical breakpoints

New clinical breakpoints are needed

- Clinical trials are missing!

MIC_{90} values are available

- These values are not sufficient to derive reliable recommendations on resistance for veterinarians
- Modelling might be applicable but strategies and other necessary pharmacological data are missing

Epidemiological cut-off values (ECOFFs) data are available

- Pharmacological data is missing to evaluate whether the necessary inhibition concentrations are achieved in the respective/infected tissues (exemption e.g. macrolides due to tissue enrichment)

Any questions?

Further information

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Coordinate Network activities to improve **data collection on antimicrobial use** in animals - stakeholder comments

Stakeholder comments

- ***Standardised collection methods** would incentivise MAH reporting. ESVAC data collection from MAHs is disharmonised and a huge administrative burden for companies.*
- ***Benchmarking of use** data will be a **more effective motivator than quantitative reduction targets** which may shift to use of more potent compounds (often CIAs).*
- ***Reduction in AMR-infections** should be the **primary endpoint**. Knowledge is lacking if quantitative reduction targets correspond to reduction in AMR, and levels of AMC to be achieved to reduce AMR development*

Actions identified by the EMA secretariat and session chairs for discussion

- Network activities to improve data collection on AMU

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Network activities to improve data collection on AMU

- How should we best utilise the data collected under the NVR – Should this be at local (for farm data) national or EU level?
- What associations should we be looking at e.g. JIACRA, AMR in target pathogens, AMR infections (*stakeholder proposal*)?
- Could industry integrate the data collected through Ceesa?