EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Demonstration of efficacy for veterinary medicines containing antimicrobials

Key developments and outcome of focus group

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Revision of the existing guideline – What has changed and why?

Original **CVMP GL** for the demonstration of Efficacy for VMPs containing Antimicrobial Substances (EMEA/CVMP/627/01) came into effect **June 2003**

Revision needed to address:

Expanding knowledge in areas affecting development of antimicrobial VMPs, e.g. PK/PD

Themes identified in **CVMP Strategy on antimicrobials 2011-2015**: Need to **maintain availability of AMs for both animals and humans** (aligned with **responsible use**)

Key issues identified in the Concept Paper

- Characterisation of the **susceptibility pattern** for target pathogens
- Use of **PK/PD** to support dosing regimens
- Application of **"responsible use principles"** to the design of clinical studies:
  - Studies for AMs regarded as **"second line"**
  - Studies for **Prevention and Metaphylaxis** claims
  - **Control groups** to be used in non-inferiority studies
  - **Diagnostic methods** and use of bacteriology
  - Duration of the **follow up period**

Comments in writing received during the consultation period (end 30 Nov 2013)

- European Group for Generic Veterinary Products (EGGVP)
- Association of Veterinary Consultants (AVC)
- International Federation for Animal Health Europe (IFAH-Europe)
- ECO Animal Health Ltd
- European Coalition to End Animal Experiments (ECEAE)
- Professor Peter Silley, MB Consult Limited & University of Bradford
- Federation of Veterinarians of Europe (FVE)

>> Focus group with stakeholders on 8 December 2013

Focus Group Meeting on 8 December 2013 - Major concerns raised by stakeholders

- Disincentives for any new product development in Europe
- Impact on the availability of veterinary medicines (referral procedures)
- Increased requirements, too complex
- Ambiguous terminology („second-line“)
- Application of responsible use principles in clinical field studies („second line“), no clear recommendations
- Control in field studies – justification of efficacy of (approved) positive control products

Other concerns

Disincentives for antimicrobial product development

The current draft discourages any new molecule development for Europe and this might impact not only on availability of new molecules, but also on further development of existing AMs and generic products. With regard to WEU products stakeholders suggested to provide a **separate guideline or modify the current draft** .

Message:

It is aimed to develop a GL that provides **viable options for product development**, whilst taking heed of **responsible use principles.** Keep in mind **Benefits** (efficacy) as well as the **AMR risks.** For variations/ extensions data requirements do relate only to the new aspects.

Unspecific terminology: „Second line“ antimicrobials

The criteria for **„second line“ classification** (Concept paper) are not clear and potentially misleading; they appear to be based primarily on the perceived public health risk.

Message:

It is agreed there is no clear definition of „second-line“, therefore, the **term is not used in the draft guideline**. The AMEG is in response to the Commission‘s request for advice currently developing a categorisation in line with the WHO list and other considerations, but this will not include definitions of first/ second line treatment.

„Second line“ - Implementation of „responsible use principles“ in a clinical field study design (sections 4 and 6.4.1)

Logistic, statistical and animal welfare problems were highlighted by stakeholders if clinical trials were to be conducted in line with a proposed **„second line“** treatment (recruitment of non responders or poor responders to 1st line treatment).

„Second line“ was considered to be a risk management measure which appears to be mainly based on perceived **public health risks.**

It was proposed to demonstrate the **intrinsic efficacy** of an antimicrobial in a „standard“ clinical trial and to address risks in relation to animal or human health due to AMR in a **separate risk assessment** and inclusion of RMMs in the SPC.

„Second line“ - Implementation of „responsible use principles“ in a clinical field study design (sections 4 and 6.4.1)

Message:

The major concern of the stakeholders in relation to the target population is acknowledged by the CVMP and it is agreed to **relax** the strict approach.

The **proposal** of the stakeholders to demonstrate the „intrinsic efficacy“ did however **not** gain **full support** by the CVMP.

Different **options** for supporting data were considered, which could be suitable for different target species, diseases and clinical situations. Further internal discussion in the EWP/ AWP is needed.

Control methods in clinical field trials (section 6.4.2) – positive control

Concern in relation to the request that the applicant should justify the efficacy of the selected (approved) reference product based on information (**new experimental data?)** about the susceptibility of target pathogens.

Message:

No requirement of **new** experimental **data**; this refers to the situation where **literature data** suggest that there is AMR for the control product. The suitability of the control should always be confirmed **prospectively** to the trial e.g. by investigating posologies in different MSs. Respective examples included in the current draft.

Characteristics of susceptibility pattern of target pathogen (section 5.3); minor

New requirements (food animals): **increased number of strains and increased information of origin of strains**)

The current text with regard to determination of **ECOFF / CBPs** needs to be clarified.

Message:

Need to **revise text** in relation to gaining isolates from different production types: Background data should be collected on origins of samples as supporting evidence, and a representative range of sites should be covered. The number of samples should be scientifically justified. Need to revise the text to make a **recommendation** on Clinical BPs, but **not a requirement**.

Dose determination (sections 6.2, 6.3); minor

i)The use of **population kinetics** in diseased animals had been criticised due to regulatory and animal welfare aspects of collecting such data;

ii)The request for testing different **dosing intervals and different number of administrations in dose determination studies** would increase the number of animals and animal groups opposing the 3R principles

Message:

i) The development of population data is **encouraged** but not required**;**

ii) **Alternative options** are described in the text which support these parameters (ref. to published data, PK/PD etc); these should be more clearly indicated.

Control methods in clinical field trials – negative control (section 6.4.2); minor

In field studies in support of a **prevention claim,** the use of a negative control group is not always possible for ethical and economical reasons and **should not be mandatory when justified**

There was also discussion how to **define the treatment** e.g. in the case of **quickly spreading** infectious agents leading to **peracute** illness of animals and where it would not be reasonable to wait until clinical signs occur. This could be regarded as prevention rather than metaphylaxis.

Message:

Point noted. However, for prevention, without negative control it can not be determined whether the treatment was necessary or not. Further discussion needed.

Metaphylaxis (section 6,4,7); minor

It appeared that stakeholders in general did support the introduction of this terminology but ask for **more specifications on what to analyse, and how in the case group/flock treatment** (e.g. statistical unit; appropriate control in clinical trials for the demonstration of treatment and metaphylaxis at the same time)

Message:

Points noted; text needs **to be revised**

Duration of post-treatment follow up (section 6.4.6); minor

Relapse and re-infection rates are a very complex area and difficult to distinguish, in particular in group treatments where there are high circulating levels of infection, development of immunity and differences between –cidal and –static AMs. This should be reflected in the guideline.

Message:

Point noted. Further discussion is needed. Maybe need to distinguish between individual and group treatment

Inclusion of a glossary in the guideline

It had been noted that the definitions for „treatment“, „metaphylaxis“ and „prevention“ are not in line with EPRUMA and other bodies. Refinement of the definitions is recommended.

Some stakeholders would like to include a glossary in the guideline

Message:

Consistency with other definitions will be checked. Glossary can be added.

Conclusion and outlook

- The Focus group meeting was very helpful, it was an open-minded, scientific discussion/ exchange between regulators and stakeholders
- The CVMP acknowledged the comments received from stakeholders and endorsed the EWP and AWP to continue the revision of the guideline
- A revised draft is intended to be available in the 3 or 4 quarter of 2014
- Whether another 3-month period for consultation will be offered, will be decided by the CVMP

Thank you for listening

Any questions?