EGGVP comments as regards the **EMA scientific recommendations** on delegated and implementing acts as part of the implementation of the new veterinary medicines Regulation 2019/6

Subject: **Criteria for the designation of antimicrobials to be reserved for certain infections in humans (Art 37(4))**

On 6 February 2019 the European Commission sent a request to the European Medicines Agency for scientific recommendations regarding the establishment of the criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans in order to preserve the efficacy of those antimicrobials, as required under Article 37(4) of Regulation (EU) 2019/6 on veterinary medicinal products.

The Committee for Medicinal Products for Veterinary Use (CVMP) adopted the scientific recommendation, which was sent to the European Commission on 31 October 2019.

The European Commission (DG Sante) has contacted EGGVP with a request for written comments as regards the EMA advice, in the context of a targeted stakeholder consultation. EGGVP highly values this consultation and the opportunity to comment on this topic; we thank DG Sante for the initiative.

Preliminary considerations

EGGVP supports the correct and prudent use of antibiotics and shares all concerns related to resistance development. Antimicrobial resistance is a complex issue that needs to be addressed **Globally** and under a **One-Health** approach, so as to preserve the efficacy of antibiotics that currently play a vital role in protecting human and animal health, while ensuring the supply of safe food.

> ***Global dimension*** **-** The latest ESVAC report[1], published in October 2019, shows that sales of antimicrobials for use in animals in Europe fell by more than 32% between 2011 and 2017. However, in other continents, the use of veterinary antibiotics and - most important – critically important antibiotics, is still increasing[2] and still includes preventive use and subtherapeutic dosing, which is in contrast to the significant positive developments already realized in Europe. This excessive and incorrect use is the main driver for antimicrobial

resistance; only with a more ambitious global action plan and international commitment it shall be possible to obtain results in fighting antimicrobial resistance.

One-Health approach – As it is well known, any effective approach to combat the rise of antimicrobial resistance shall be based on holistic stewardship programs, including veterinary medicine, human medicine and agriculture. While it is recognised that EU action has led to some progress especially on veterinary and food related issues[3], prudent use, restrictions and use of effective alternatives should be further stressed and implemented in all concerned sectors. Recent reports[4] in Europe show that the use of critically important antibiotics has increased in people while has been drastically reduced in animals. It is regrettable that all efforts on the veterinary field have not been accompanied by equal efforts in all sectors.

Applying severe restrictions and prohibitions on the use of certain antibiotics in a particular field (animal health) and in a sole geographic area (EU) may not only be ineffective and unrealistic, but it may also entail negative consequences - for animal health and welfare, with associate increase of suffering and death, and also for public health (higher use of alternative antibiotics that increase resistance patterns and/or that are less effective) and for the environment (when alternatives to banned products are more detrimental for the environment).

While EGGVP understands this is beyond the mandate to the Agency and its advice, these are basic but most important considerations and as such EGGVP would have appreciated the advice to be adequately contextualized.

Comments on the EMA advice

- The advice is well written; the principles are correctly designed, logically and intelligibly described, covering a wide range of EU and international guidelines, standards and regulations.

- The considerations for the selection of criteria (section 3) have a balanced approach towards human and animal health, which is welcome.

  However this fair approach is missing under section 3.2. (resistance transfer), stating that a greater impact from transmission of resistance between animals and humans is expected to occur. Recent studies suggest that the clinical issues with antimicrobial resistance in human medicine are primarily the result of antibiotic use in people, rather than the use of antibiotics in animals[5]. The clones that are responsible for most of the antimicrobial resistance problems in humans and animals are largely distinct, and there is no current evidence that pathogens from a One-Health reservoir cause disease in European hospitals in substantial numbers[6]. Literature also indicates that, despite significant decrease of use in animals, there is still a very high prevalence of resistant pathogens, which shows that the reduction in antimicrobial

has not (yet) had any positive effects[8]. Additionally, recent findings suggest that socioeconomic factors, mainly sanitation and health, seem to be the main driver of resistance in healthy humans[8]. All these factors should be reflected so as to provide a broader and more balanced overview based on actual scientific evidence.

- It is unclear to what extent the aspects discussed in the EMA advice will find their way into the legislation. It is our understanding that only section 4. "Criteria retained" is intended to be included in the secondary legislation. Likewise, the acknowledgment that the designation of antimicrobials for human use only is the most severe risk management measure which should be used with discretion, and that other risk management measures exist that can be applied to preserve the efficacy of antimicrobials in human medicine, is not expressed in the proposed criteria. EGGVP is of the opinion that in the legislation the proposed criteria should be preceded by risk management measures that should be applied on a case-by-case basis before considering reserving an antimicrobial/antimicrobial class for human use.

- EGGVP supports initiatives and measures based on risk assessment and thorough scientific evaluation. Criteria should be designated based on quantifiable parameters whenever possible. It is paramount that criteria and methods applied provide irrefutable evidence that the use of a certain antimicrobial (or class) in veterinary medicine is substantially and measurably contributing to an increase of resistance in humans (and as such should be subject to prove evidence).

  EGGVP's concern is that « Criteria retained » (section 4) are not always sustained by measurable parameters. We also regret that provisions and terminology in this section are often too vague and provide uncertainty and unpredictability. The full section 4 should be revised to provide the necessary precision and elements to perform a scientifically sound evaluation. Specific comments on each criterion:

  Criterion 1 - High importance to human medicine

  - "Limited few alternatives" and "Limited treatment options": „limited" should be defined (number of minimum required alternatives).
  - The advice should reflect that use of the specific antibiotic must be safe, without serious adverse effects in human beings. Furthermore, criteria should be supported and reviewed by scientific and clinical/practice evidence; as such treatment effectiveness in humans shall be reported, monitored and analysed.

  Criterion 2 – Risk of transfer of resistance

  - First condition: parameters to define a „significant" contribution of transmission should be established. Scientific measurement of transfer is required.

- Second condition: minimum requirements for "existing data" to be considered as acceptable should be set.
- It is not clear if the two conditions need to be met simultaneously to fulfil the criteria. As per subsequent decision trees (section 5) we assume this is not the case.

Criterion 3 – Low importance to animal health

- Advice should state that available alternatives (antimicrobials or other alternative management strategies) should not pose a risk of worsening the resistance patterns (i.e. increased use of other critically important antibiotics or increased use of antibiotics with a risk to potentially increase co-selection), which will have counterproductive results for public health. The available alternatives should also not pose a (higher) risk for the environment.
- First condition: parameters to define what is considered „significant morbidity and/or mortality" are needed.
- Second condition: Veterinarians have to have access to effective antibiotics in treating bacterial diseases in their praxis for food-producing and/or companion animals. Severe restrictions in use could have unacceptable consequences for animal health and welfare in the cases where there is no effective and appropriate alternative. As such we recommend to replace „alternatives" by „effective alternatives", as well as to precise the number of minimum required alternatives to meet the condition.
- It is not clear if the three conditions need to be met simultaneously to fulfil the criteria. As per subsequent decision trees (section 5) we assume this is not the case.

➢ While the EMA advice provides considerations for the selection of the criteria, including differences between food producing and companion animals and impact of the pharmaceutical form are discussed, not all these considerations appear to have been incorporated into the proposed criteria in section 4. Before applying restrictive measures to a full category of antimicrobials, further stratification should be considered taking into account elements such as target animal species, indications, individual product specificities, type of treatment (herd vs individual), and administration route, i.e.

- *Target species:* the proposed criteria give rise to concerns that differences in use of antimicrobials in food producing and companion animals may be disregarded and an increased risk of e.g. transfer of resistance in one pool of animals results in a general ban even though in another pool of animals the risk is considered low.
- *Route of administration*: topical and local routes, such as intramammary, ocular, ear, cutaneous… generate less antimicrobial resistance than systemic routes. There is major concern that this is not considered, with the risk to suppress important molecules only used topically and much needed by veterinary practitioners (it is important to note that few molecules are available to treat topical infections). EGGVP recommends referring to

draft CVMP proposal listing of routes of administration and formulations, ranked in order from those with in general lower effect on the selection of AMR to those that would be expected to have higher impact on resistance (EMA/CVMP/CHMP/682198/2017, page 17).

- *Product specificities*: for some antimicrobials, besides being administered systemically, no absorption takes place after oral use (so having local intestinal activity only) and dissemination throughout the entire body is absent. This further results in highly effective doses only there where it is needed. As such these properties reduce the risk of development and transfer of resistance. Furthermore, a specific general method of action, without targeting a very specific receptor, can result as such in the absence of the development of significant resistance.

All this comes in support to our previous statement that criteria should be preceded by thorough risk assessment and risk management measures to be applied on a case-by-case basis

- In section 5. "Using the criteria" different approaches are proposed depending on the authorisation status of the antimicrobial substance. While for substances that are currently only authorised for human use (5.1) and substances not currently authorised for medicinal use at all (5.4), the possibility to introduce restrictions/measures sufficient to preserve human health rather than an immediate inclusion in the reserved list is provided in the decision tree, for antimicrobials authorised in veterinary medicine, only existing restrictions/measures to preserve human health are taken into consideration. There may however still be further measures available to preserve human health before a complete ban becomes necessary. We therefore propose the following amended wording to be included in the decision trees for antimicrobials only authorised in veterinary medicine (Figure 2 of the Advice) and antimicrobials authorised in human and veterinary medicine (Figure 3 of the Advice):

  Current wording: Are existing restriction/measures sufficient to preserve human health? – Consider existing restrictions in the Marketing Authorisation

  Proposed wording: Are existing restriction/measures sufficient or could other restrictions/measures be sufficient to preserve human health? – Consider existing and potential restrictions in the Marketing Authorisation

  Last but not least, under section 5 (figures 1, 2, 3 and 4), decision is to be made based on a "potential risk for transmission". This is not in line with criterion 2 (section 4.2.) where a „significant" contribution of transmission is determining the condition. The text in figures under section 5 should be amended accordingly.

- Annex 3 lists the main pathogens/disorders for which antimicrobials are mostly used (EMA/EFSA, 2017 Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA) as

a reference). While the list is considered to be very complete for most species, it has been pointed that gastrointestinal disorders such as enteritis caused by *E.coli* in turkeys are common but not listed in Annex 3. EGGVP suggests including this disorder under relevant category in page 61.

Recommendations for the future list

According to Article 37(5) of the new veterinary regulation, the Commission shall, by means of implementing acts, designate a list of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans.

- **Mechanisms to ensure periodic updates, dynamic list**

  The epidemiological situation is in complete evolution, and resistance patterns may change very rapidly both in the human sector and the livestock sector. Monitoring and surveillance in order to evaluate that any established measures continue to be adequate shall be established, with appropriate mechanisms to ensure the list will be revised periodically.

  As a consequence, the future list of antimicrobials to be reserved for human use must be dynamic and evolve according to available scientific data, considering the national, European and global contexts, in the human and the veterinary side simultaneously, while monitoring any new bacterial resistance development and evidence are important elements of the decision making process.

  Moreover, it should be possible to reconsider or revise certain non-effective measures or restrictions, especially in cases when the restriction of the use of an antibiotic group might lead to overuse and pronounced resistance development in another group, which would obviously require change in the reserved list for the future.

- **Post-management measures:** There is an ethical obligation to care for diseased animals. Antibiotics save animals from disease, suffering and death. Antibiotics also ensure that food comes from healthy animals and is, therefore, safe for humans. It is important for both animal welfare and public health that veterinary surgeons have access to antibiotics which are effective in treating bacterial diseases.

  Decision to use an antibiotic shall remain under the veterinary decision and based on laboratory test that support the diagnosis, susceptibility testing and history of the herd that indicate that certain antibiotics are effective (or not).

  The future list should make clear any possible post-management measures (i.e. total ban, including off-label, use in special circumstances allowed... - e.g. life threatening illness, when susceptibility test has shown that no other alternative could be effective).

References

[1] European Medicines Agency
Ninth ESVAC report, Sales of veterinary antimicrobial agents in 31 European countries in 2017, Trends from 2010 to 2017

[2] US Food and Drug Administration
2018 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals (showing 9% increase sales of medically important antibiotics)

[3] European Court of Auditors
Special report No 21/2019: Addressing antimicrobial resistance: progress in the animal sector, but this health threat remains a challenge for the EU

[4] UK Veterinary Medicines Directorate, Food Standards Agency, and Public Health England
UK one health report: joint report on antibiotic use and antibiotic resistance, 2013-2017 ((showing that the use of critically important antibiotics increased in people by 8% and decreased in animals by 51% between 2013 and 2017).

[5] Alessandro Cassini, MD, Liselotte Diaz Högberg, PhD, Diamantis Plachouras, PhD, Annalisa Quattrocchi, PhD, Ana Hoxha, MSc, Gunnar Skov Simonsen, PhD, et al.
"Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis"
The Lancet, VOLUME 19, ISSUE 1, P56-66, JANUARY 01, 2019

[6] Hajo Grundmann, University of Freiburg - Medical Centre
Presentation *"Drivers of the AMR epidemic in Europe at the human and OneHealth interface: Searching for the smoking gun."*

[7] Dierikx CM1, Hengeveld PD1, Veldman KT2, de Haan A1, van der Voorde S3, Dop PY3, Bosch T1, van Duijkeren E4.
"Ten years later: still a high prevalence of MRSA in slaughter pigs despitea significant reduction in antimicrobial usage in pigs the Netherlands"
J Antimicrob Chemother. 2016 Sep;71(9):2414-8. doi: 10.1093/jac/dkw190. Epub 2016 Jun 3.

[8] Prof Peter Collignon, PhD, John J Beggs, PhD, Prof Timothy R Walsh, DSc, Sumanth Gandra, MD, Ramanan Laxminarayan, PhD
"Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis"
The Lancet, VOLUME 2, ISSUE 9, PE398-E405, SEPTEMBER 01, 2018