animalhealth europe | THE VOICE OF THE ANIMAL MEDICINES INDUSTRY

Position paper

Final 19th December 2019

AnimalhealthEurope comments to the scientific advice on criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans.

EMA Advice on implementing measures under Article 37(4) of Regulation (EU) 2019/6 on veterinary medicinal products

1. General Comments

AnimalhealthEurope welcomes the opportunity to provide comments to the EMA Scientific Advice. The advice appears a well-balanced, scientifically sound analysis of international standards and EU Member State and third country legislation on categorisation of antimicrobials, with both veterinary and human health aspects taken into consideration.

Considering the science based and balanced approach, considering the EMA advice takes into account both Human and Animal Healthcare needs, and bridges these needs by a demand for a scientific assessment of the transferal of resistance from Animals to Humans, we strongly support the adoption of the EMA advice into the Delegated Act and we recommend that additional advice is sought from the EMA on the details specified below to clarify how the criteria will be implemented.

Transparent and predictable assessment

Whilst supporting the approach in general terms with the 3 criteria to help guide their use, the current wording is such that there remain many ambiguities, particularly in criterion 2, and it is essential that these are addressed to ensure a fair, transparent, science-based (considering all available relevant published literature) and predictable assessment. See later comments on 4.1-4.3.

For example, it is noted that throughout the document the term 'significant' is frequently used for example '…risk the transfer of antimicrobial resistance from animals to humans is considered as significant…' without any quantification. What is meant by significant in this sense, or elsewhere? It would be more helpful if the risk could be further quantified with terms such as very low, low, medium, high or very high throughout the document and with an indication as to how this is calculated.

Major points of emphasis

As a last resort in the risk management of antimicrobial resistance

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The advice of preserving an antimicrobial for human use only should be considered as a last resort in the risk management of antimicrobial resistance. Three risk management options (limit use outside the terms of the marketing authorisation, restriction of use in the MA and establishing conditions for use) are provided, focussed on using the terms of a marketing authorisation to limit the use of antimicrobials. In this respect, scientific evidence for the usage and/or restrictions on usage should be considered in the decision-making process and be published. This will enable the veterinarian to make a science-based assessment on which antimicrobial to use that is in the best interest of animal health, food safety and wellbeing combined.

Support for science-based decision-making

The advice has at its centre science-based decision-making to protect both human and animal health. This is strongly supported by the animal health industry. Our comments below underline the need for further specification of the scientific evidence needed for the decision-making process. We urge the European Commission to elaborate further on the path of science-based decision making in drafting the delegated act.

The starting point should be on the individual high-risk human pathogens

Rather than starting with individual antibiotics, the starting point of each decision tree and the focus of the evaluation should be on the individual high-risk human pathogens (i.e. life-threatening diseases). The pathogens that are to be in scope and to be taken through the decision trees must be clearly defined following advice from ECDC; they should be published and reviewed and updated as necessary. The overall risk for humans resulting from the use of antibiotic substances in veterinary medicine should be evaluated by risk assessment following transparent criteria and decision trees yet to be fully elaborated and clarified.

We call upon the Commission when presenting the draft list of antibiotics substances to be reserved to present for each substance considered the full detailed evaluation against the criteria and how the criteria were applied. This should include, for example, the human pathogens considered for each substance, the information considered on resistance and demonstration of links to pathogens found in animals and how they weighed up the importance of the antibiotic to treat animal disease.

Criterion 1:

Greater clarity is required concerning terms such as “limited few alternatives”, “significant mortality” – please see specific comments.

Criterion 2:

There is very little to no scientific information or guidance provided in this document regarding how the risk of resistance transfer will be assessed, especially in terms of a quantitative risk assessment which is clearly implied in the EMA’s advice. It is noted that the term “risk assessment” is not used by EMA in the paper

and that paragraph 5 on the use of the criteria does not provide any guidance or direction on how the risk of resistance transfer can be assessed. *In short, clarification is required on how the transfer of resistance should be assessed*.

The criterium of "risk of transfer of resistant bacteria or resistance genes" lacks the consequences of such a transfer. For example there are at least two very different situations: (a) the transfer of a resistant pathogen, capable of causing serious disease in humans and with a high likelihood of human disease, where the majority of human infections come from animals and where effective treatment with antibiotics is essential, and (b) the transfer of resistance genes which may be subsequently transferred to a pathogen where clinical disease in humans is usually not treated with antibiotics or where animal origin resistance genes / resistant bacteria make only a small contribution to the disease burden in the human population. These two different situations and other intermediary situations, and their consequences, should be taken into account.

In applying the criterion "risk of transfer of resistance" in Figures 1-4, it appears that the final risk is categorised as 'yes' or 'no', and, contrary to the title, this is not in fact a representation of 'risk'. While Section 4.2 provides some information of how an antimicrobial agent or antimicrobial class meets this criterion of 'risk of transfer of resistance', there is no proposal for definitions of what (types or extent of) data are sufficient to meet the defining thresholds for the following:

- *Transmission of bacteria resistant to the antimicrobial/antimicrobial class or transmission of genes conferring resistance to the antimicrobial/antimicrobial class from non-human sources to humans is significant and linked to the use of the antimicrobial/antimicrobial class in animals*
- *Data exist to show the actual emergence, dissemination and transmission of resistance to this antimicrobial/antimicrobial class following use in animals or, in case the antimicrobial is not authorised for animals, data exist to show the potential of emergence, dissemination and transmission of resistance.*

As such, without more specification regarding the types and extent of data needed, the "risk of transfer of resistance" appears to be the same for all antimicrobials. This is because, considering that cross- and co-resistance is applicable to many antimicrobial classes, they would all be categorised as "YES" in all cases (Figures 1-5), regardless of whether the antimicrobial agent or class is categorised as high or low risk of transfer of resistance genes or resistant bacteria, whether vertical or horizontal transmission to humans occurs, and regardless of route from animal source to human, (and regardless of human health consequence for such transmission). Also, the document lacks clarity as to whether both of the above conditions (bullets) must be met, for a final categorisation of "YES", or whether one bullet is sufficient. What is an example of an antimicrobial agent (and the types of data needed) in Figures 1-4, where the "risk of transmission" was "NO"?

Criterion 3:

The consideration of the needs of the veterinary sector and the inclusion of an assessment of the impact on both animal health and welfare is a very welcome and indeed essential step. We also appreciate the acknowledgement that treating animals for disease may have a positive benefit on human health.

Throughout the document there is some inconsistency in the use of "antimicrobial", "antimicrobial class" and "antimicrobial/antimicrobial class". It is recommended that this is reviewed. However, we firmly believe that reservation must be at the substance, rather than class level.

2. Specific Comments:

Page Number/Paragraph	Comment
Page 3 / Para 4	There is no recognition that the consequences of the transfer of resistance genes or resistant bacteria can vary widely. Suggest amending to read "…from animals to humans is considered as important, the contribution and consequences of that transfer may have serious adverse health implications, and for which…"
Page 3 / Para 11	This document relates to animal use of antibiotics and not all non-human use of antibiotics. It is therefore inappropriate to broadly refer to 'non-human sources' – this should be replaced throughout the document with 'animal derived sources' or some other similar designation (except where the contents of other published documents refer to non-human use).
Page 3 / after Para 11	Suggest a new bullet point to address the consequences of transfer of resistant bacteria / genes to humans in line with the points made under General Comments (above) • Resistance is of clinical relevance in human health and the animal source is shown to make an important contribution to the burden of disease / resistance genes in human health.
Page 4 / Para 4	Expand to include resistant bacteria. Amend to read "…life-threatening infections in animals, including those caused by resistant bacteria, which if left untreated…"
Page 4 / Para 5	Expand to include resistant bacteria. Amend to read "…treatment of serious life-threatening infections in animals, including those caused by resistant bacteria."

Page Number/Paragraph	Comment
8	"According to the Regulation, 'antimicrobials' include antibiotics, antivirals, antifungals and antiprotozoals. The criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans have been developed primarily with antibacterial substances in mind, but in principle could also be applied to other types of antimicrobials." We do not believe the criteria or the use of these should be applied to substances other than antibiotics. If the principles are followed for other antimicrobials there is a high-risk innovation will be stifled. Further, the need to consider reserving other substances should only be made IF there is new evidence of a serious risk to public health.
Page 8 / Section 2.2.1	For some of the different categorisations produced by different organisations the details of the different antimicrobials / antimicrobial classes are provided e.g. "WHO model list of Essential Medicines" whereas for others e.g. "Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia", they are not (even though the details are provided in the annex). For consistency and to aid the reader it is recommended that the full lists are provided in the body of the document and the annex.
Page 8 / Section 2.1.1.4	Other risk profiling for example for the removal of growth promotion claims for medically important antibiotics, the changing of prescription status for certain antibiotics have also been performed by the FDA CVM – for completeness, these could be listed.
39	Transfer of resistance through emissions in the environment. This is most likely correct but would be rather challenging to assess to its impact. A quantification would be required in this regard to assess whether it is significant or adds up with other transmission routes to a significant level. See also comments made under General Comments and against page 44
40	5. Transmission route Clarity on the method of risk estimation and (animal use) contribution to the decision-making process is needed
Page 40 / after para 3	Two important criteria are missing in terms of assessing the impact of the transmission of resistance between animals and humans (as identified in General Comments above) and suggested wording is provided below: 7. The impact of the transfer of resistance determinants between animals and humans will be greater when antibacterial treatment is essential to effectively treat a serious disease in humans (caused by the resistant bacteria or complicated by the transfer of resistance genes to a human pathogen). On the other hand, the impact is less when the resulting disease is of either less severity or antibiotic treatment is less important in the effective treatment of the disease. 8. The impact of the transfer of resistance determinants between animals and humans will be greater when the contribution made by this transfer from animals is a higher proportion of the overall disease burden in humans due to this pathogen. Similarly, the impact will be much less when the transfer, although present, makes only a small contribution to the overall burden of disease in humans.

Page Number/Paragraph	Comment
Page 41 / para 4	Other food producing animal examples of multi-drug resistant bacteria are the *Mannheima haemolytica* which has recently been isolated from cases of bovine respiratory disease in Belgium (Van Driessche L et al 2018 Ninth International Conference on Antimicrobial Agents in Veterinary Medicine in International Journal of Health Animal Science and Food Safety 4 – 3S) and also multi-drug resistant strains of *Brachyspira hyodystenteriae (e*.g. Duinhof T et al (2008) Multiresistant *Brachyspira hyodysenteriae* in a Dutch sow herd. Tijdschrift voor diergeneeskunde. 133. 604-8).
43/3.3.2 Last paragraph	This fails to acknowledge that "authorisation status of medicinal products in the EU" is not a simple authorised/not authorised since it depends on the country, as many of the antibiotic veterinary medicines are nationally authorised.
44 4.1 High importance to human health	"Limited few alternatives", "Limited treatment options" – further explanation is needed to better define these terms, for instance how few is limited? Does it relate to just one Member State or multiple Member States? "Significant mortality…" – further clarity on how this would be determined would be helpful "serious, life-threatening infections in humans" – which ones will be considered? "In the second bullet it refers to "drug resistance", but presumably this must mean "multidrug resistance".
44 4.2 Risk of transfer of resistance	Do both bullet points have to apply? It is believed that it should be "and". "is significant" – how is this defined? Transfer of resistance has to be assessed to its significance. This clearly implies a quantitative risk assessment for which to our understanding no guidance is available. This is a major issue as clear guidance would be required to make this assessment. The document keeps completely silent about this matter. "existence of data" – what are the conditions for the data to be considered robust and valid? For example, EU data? Data from peer reviewed scientific publications? The paragraph after the two bullet points starting "generally", seems to partially offer how ranking will be approached, but insufficient detail is given. However, if a pathogen by pathogen approach in the decision trees is used this paragraph is redundant?
44 4.3 Low importance to animal health	It is not clear if all three bullets have to apply? Presumably they do. "significant morbidity", "major impact – how are these defined? Please see the point made under General Comments. "alternatives exist"," alternative management strategies" – this implies more than one, but does it relate to an individual member state and the products they have authorised/available? It should do. Unless an antibiotic product is authorised and marketed in a particular country, due to the need for an early initiation of treatment, awaiting import of an antibiotic from another member state where it is authorised and available is not viable.

Page Number/Paragraph	Comment
Page 44 / after para 7	As recommended above suggest a new bullet point to address the impact of resistance transfer and the relative contribution of resistance transfer from animals to the overall burden of disease in humans (this is partially reflected elsewhere in the document e.g. section 5.1.1, but not included as a criteria): • Resistance is of clinical importance in human health and the animal source is shown to make a scientifically clearly demonstrated important contribution to the burden of disease / resistance genes in human health.
Page 44 / last paragraph	Recommend recognising that resistant pathogens can cause problems in animals (as has been earlier discussed in the document): amend to read "…is not essential to treat a serious, life-threatening infection (including those caused by resistant bacteria) in animals…"
Page 45 / para 1	Recommend recognising that resistant pathogens can cause problems in animals (as has been earlier discussed in the document): amend to read "…the treatment of serious life-threatening infections in animals (including those cause by resistant bacteria)."
45/5	"Sections 5.1 - 5.4 include preliminary approaches which, following experience from its application, might need further refinement." The experience mentioned is presumably in development of the draft list of substances to be reserved for human use. It is important that in the secondary legislation the criteria and the way they are used are fixed, so they are predictable, and companies can plan accordingly.
p.45 /5.	It is also stated that other tools (biosecurity etc.) are important in the limitation of use of antimicrobials. This is correct but should be placed elsewhere and not under the paragraph "using the criteria". This could be misleading as it implies that these other measures have a bearing in the assessment of the three criteria.
p.45 / 5.	It is stated that criteria may be adapted depending on data available. This is very vague and open for wide interpretation. This "opening clause" could seriously dilute the proposed concept, this is why this sentence should be deleted. It could be replaced by a note that e.g. lack of data should be adequately considered in the assessment or the like.
45/5.1	"Antimicrobials only authorised in human medicine" This is understood to mean there is an MA for human use in one or more MS in the EU for a product containing the antibiotic substance in question and there is no MA anywhere in the EU for veterinary use of a product containing this antibiotic substance. It is suggested this is clearly set out. (Similar comments apply to clarity of the headings for sections 5.2, 5.3 and 5.4).
Page 45 / para 11	In relation to antibiotics not authorised in either human or veterinary medicine (which has not been discussed earlier in the document), another criterion should be introduced which is not otherwise discussed or its value recognised in this document. This criterion was described in Answers to the request for scientific advice on the impact on public health and animal health of the use of antibiotics in animals EMA/381884/2014 "The authorisation of completely new classes of antimicrobials for use in animals might decrease animal and public health risk related to antimicrobial resistance provided co-selection by earlier authorised products are not implicated."

Page Number/Paragraph	Comment
46 to 49	The comment applies to all figures in this paragraph. Under the heading "risk of transfer of resistance" the question is phrased whether there is a potential risk (which in fact means a hazard, not a risk) and not whether there is a significant risk. Thus, the figure does not correctly reflect what has been outlined on p.44/4.2. This can be very misleading and should be corrected. Practically, for all compounds or classes a potential risk of transmission or cross-resistance would be difficult to fully exclude.
Page 46 / Figure 1	The question "Risk of transfer of resistance" should be retitled (as discussed above) to "Risk, consequence of transfer and relative contribution to resistance in human medicine". Additional subpoints should be added "AND, is there a serious consequence in human medicine to transmission?" "AND, is transmission from animal sources proven to cause an important proportion of the overall burden of disease in human health?" i.e. all 3 criteria would need to be established for "YES"
46	In this case, the potential risk for transmission of resistance (including the potential for cross-resistance) should be assessed. The assessment should be based on scientific proof.
Page 47 / Figure 2	It is not clear why "potential" has appeared in "Is there a potential need…". The concern is that there is always a 'potential need but either there is an actual need or there isn't an actual need at the current time. Recommend deletion of "potential" and change this to specify "an identified need". A precautionary approach by Human health to leave all possible future options open in case of an event that can't be envisaged today has to be avoided.
Page 47 / Figure 2	The text "(Probably no interest for humans)" appears to be placed against the wrong arrow "YES" and should be placed against "NO" i.e. immediately not included in reserve list (otherwise this doesn't make sense).
Page 47 / Figure 2	The question "Risk of transfer of resistance" should be retitled (as discussed above) to "Risk, consequence of transfer and relative contribution to resistance in human medicine". Additional subpoints should be added "AND, is there a serious consequence in human medicine to transmission?" "AND, is transmission from animal sources proven to cause an important proportion of the overall burden of disease in human health?" i.e. all 3 criteria would need to be established for "YES"
Page 48 / para 2	Recommend change to read (consistent with points made above): "… Data are available and enable the assessment of the risk, impact and relative importance of the risk of transfer of resistance and cross-resistance."
Page 48 / Figure 3	The question "Risk of transfer of resistance" should be retitled (as discussed above) to "Risk, consequence of transfer and relative contribution to resistance in human medicine". Additional subpoints should be added "AND, is there a serious consequence in human medicine to transmission?" "AND, is transmission from animal sources proven to cause an important proportion of the overall burden of disease in human health?" i.e. all 3 criteria would need to be established for "YES"

Page Number/Paragraph	Comment
Page 49 / after para 1	Consistent with points made above in Answers to the request for scientific advice on the impact on public health and animal health of the use of antibiotics in animals EMA/381884/2014 "The authorisation of completely new classes of antimicrobials for use in animals might decrease animal and public health risk related to antimicrobial resistance provided co-selection by earlier authorised products is not implicated.", there is another source of value for society if the antimicrobial is an antimicrobial class which would have little or no utility in human medicine. This should be introduced as point 4.
Page 49 / Figure 4	The sub-question under Risk of transfer of resistance: "Is there a potential for transmission – cross-resistance potential?" is too simplistic because if a new antibiotic from a new veterinary only class of antimicrobials was authorised then if resistance was seen, obviously transmission could occur to human medicine, but there would be no consequence to this transmission and it would only be after incorporation in plasmids or other similar elements that co-resistance would become a concern. The question could be better worded "Is there a potential for co-resistance which would impact on the identified potential use of the antibiotic to treat serious disease in people"
Page 49 / Figure 4	The question "Risk of transfer of resistance" should be retitled (as discussed above) to "Risk, consequence of transfer and relative contribution to resistance in human medicine". Additional subpoints should be added "AND, is there a serious consequence in human medicine to transmission?" "AND, is transmission from animal sources proven to cause an important proportion of the overall burden of disease in human health?" i.e. all 3 criteria would need to be established for "YES"
49/ 5.4	"For any intended future submission of an application for the establishment of maximum residue levels or a marketing authorisation for a new antimicrobial for veterinary use, a specific process should be put in place in order to assess the antimicrobial against the criteria for the designation of antimicrobials to be reserved for human use." This implies some form of mandatory process prior to MRL or MA application submission. Presumably this relates to the CVMP paper on preliminary risk profiling. AnimalhealthEurope supported this as an option for companies and highlighted the timing of this is critical i.e. level of risk of a negative decision and hence reluctance to perform expensive clinical studies versus having sufficient data available to demonstrate benefits and future importance to animal health.