Introduction to comments by PAHC

PAHC supports comments submitted separately to this matter on behalf of the animal health industry by AnimalHealthEurope.

In addition, PAHC provides these compound specific comments largely relating to the streptogramin class of antimicrobials, for which PAHC has particular knowledge and interest.

PAHC is the sole global supplier of the streptogramin compound, virginiamycin. Virginiamycin is an important agent approved for therapeutic use in most major food producing countries for necrotic enteritis of poultry, liver abscess of cattle and swine dysentery. Virginiamycin is not approved for use in the EU, however, as an initial step to EU market authorization PAHC made a human food safety submission to the EMA to support the establishment of poultry MRLs. MRLs for poultry species were established by the EMA (2015) and subsequently adopted by the EU (EMA/CVMP/643658/2014).

> "On 3 September 2015 the European Commission adopted a Regulation establishing maximum residue limits for virginiamycin in poultry species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use."

PAHC notes in the "Terms of reference and scope" section of EMA/CVMP/643658/2014 it is stated:

> The request is further linked to Article 118(1) of the Regulation which states that third countries will also have to respect the restrictions imposed on the use of antimicrobials in animals in the European Union. The prohibition on use of antimicrobials designated in accordance with Article 37(5) will also apply to animals or products of animal origin exported from third countries to the Union.

PAHC notes in the EMA Antimicrobial Expert Group's 2017 report (AMEG-17) described the streptogramin antimicrobial class as "considered obsolete" with respect to human medicine. In the same report using mechanical process (that is, not being supported by human health needs) reflective solely of the current veterinary marketing status of the class, AMEG-17 placed the streptogramins in "Category A", the most restrictive AMEG category. PAHC previously submitted detailled comments on this categorization as part of the public comment process relating to the AMEG document, so other than drawing attention to those comments will not reiterate those comments in this document.

Comments to EMA/CVMP/643658/2014

PAHC notes the EMA as referenced the AMEG categorization, in addition to that of the WHO and a number of national governments.

It is not clear to PAHC how the EMA proposes to utilize these references to determine which antimicrobial classes should be reserved for the treatment of certain infections of humans. In particular whether the AMEG report will carry additional weight as this group was convened by the EMA.

The principle underlying the reservation of antimicrobials for exclusive human use is premised on conserving agents necessary for the treatment of important human diseases. Accordingly, PAHC strongly encourages the EMA not to include the streptogramin class, "considered obsolete" by AMEG in the group reserve for human only use, simply because this class does not have an agent currently approved for veterinary medical use in the EU.

Noting the specific relevance of this restricted list to third countries, any restriction on streptogramins, specifically virginiamycin, could create an unnecessary restriction in apparent contravention of the SPS provisions applicable to international trade. Again we specifically note the AMEG scientific comment that the class is "considered obsolete", in the placement in AMEG Category A is solely based on the absence of a current veterinary registration in the EU, notwithstanding the 2015 promulgation of EU MRLs following a favorable EMA scientific report.

The only other general comment PAHC wishes to make in the submission relates to the medical importance categorization of streptogramins by other national governments.

Specifically, the categorization of "High Importance" in Canada is based on the class being "a preferred option for treatment of serious human infections". This categorization was published in 2009. Since that time the approval of Synercid, the human use streptogramin has been withdrawn in Canada and no other streptogramin is approved in that country. Consequently, PAHC asserts that more appropriate categorization that country would be Cat III (Medium) or more appropriately Cat. IV (Low) based on this countries own criteria.

Similarly the USA categorization was published in 2003 when it was hoped that Synercid would be an effective therapy for vancomycin-resistant Enterococcus faecium (VREf). Since that time the US-FDA required to sponsor remove the label claim for VREf therapy due to lack of supported effectiveness.

While the review of categorization of antimicrobial classes according to their medical importance is in principle a dynamic process, the speed of speed of reclassification is considerably faster when evidence is driving additional restriction. Where the evidence supports lesser importance to human health the process is often considerably slower. PAHC strongly believes that globally the streptogramin class will be progressively ‘declassified’ reflective of its lack of importance to human medicine, although we acknowledge the process is exceptionally slow.

We strongly encourage the EMA not to recommend the reservation of the streptogramin class class, “considered obsolete” in human medicine, for exclusive use in human medicine.

Continuing to allow the class to be used internationally as a therapeutic agent for the important veterinary diseases: necrotic enteritis in chickens, liver abscess in cattle and swine dysentery, and potentially for these diseases in the European Union in the future will benefit not only veterinary health and welfare, but human health through the provision of high quality food and the avoidance of the use of truly important antimicrobials for these veterinary diseases.

PAHC thanks EMA for the opportunity to make these comments, and remains available should the agency require any additional information or clarification with respect to our comments or the streptogramin class of antimicrobials.

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