Divergent position on a CVMP opinion on an Article 35 of Directive 2001/82/EC for Veterinary medicinal products containing a combination of lincomycin and spectinomycin to be administered orally to pigs and/or poultry (EMEA/V/A/110)

We, the undersigned, have a divergent position on the outcome for the Article 35 procedure for veterinary medicinal products containing a combination of lincomycin and spectinomycin to be administered orally to pigs and/or poultry. The divergent position concerns specifically powders for use in drinking water and particularly the indications for chickens, namely:

“For the treatment and metaphylaxis of chronic respiratory disease (CRD) caused by Mycoplasma gallisepticum and Escherichia coli, and associated with a low mortality rate. The presence of the disease in the flock must be established before the product is used.”

First of all, the part “associated with a low mortality rate” is indicative for a limited level or poor efficacy for these combination products. All other indications for other animal species (pigs) for these products are only for gastrointestinal indications that cause diarrhoea. This is due to the fact that the spectinomycin portion of the combination is not appreciably absorbed from the gastrointestinal tract and thus mostly active within the gastrointestinal tract. However for chickens, these veterinary medicinal products only describe non-gastrointestinal indications involving respiratory tract infections. Therefore, it is difficult to understand as to how it can be justified that a combination product (e.g. lincomycin/spectinomycin) can have the indication for respiratory tract infections, when one of the active substances (spectinomycin) is not absorbed nor accumulates to clinically relevant therapeutic concentrations within the respiratory tract. E. coli is generally not susceptible to lincomycin and there is no clear evidence as to how spectinomycin should be efficacious against E. coli within the respiratory tract. This has led to different hypotheses, in order to maintain the indication of respiratory E. coli based on:

- Lincomycin may have bacteriostatic effects on respiratory and septicemic types of sensitive E. coli.
- Spectinomycin can reduce the environmental shedding of E. coli that can contribute to the flock outbreak, and thus justifying a combination product for this indication.

Since spectinomycin is not appreciably absorbed from the gastrointestinal tract, then the main premise of its role in chicken colibacillosis is to prevent or reduce the spread of E. coli from either the gastrointestinal tract or environmental/inhalation sources. In this context, there is no direct therapeutic role for spectinomycin in chicken colibacillosis, but only an indirect role to reduce environmental sources of E. coli as a non-prudent use of an antimicrobial.

The main justification for the role of spectinomycin for respiratory infections in chickens comes from Goren et al., 1988 who observed high efficacy or oral lincomycin-spectinomycin in treating experimentally induced E. coli in chickens, despite the absence of any antimicrobial activity in the serum of these chickens (Goren E et al. 1988 Therapeutic efficacy of medicating drinking water with spectinomycin and lincomycin-spectinomycin in experimental Escherichia coli infection in poultry. Vet Q 10:191.). However, Goren et al., 1988 used an analytical method with a low sensitivity, and other literature data (Abu-Basha EA J Vet Pharmacol Ther. 2007 30(2):139-44).
have shown a very low oral bioavailability of 11.8-26.4% of spectinomycin in broilers. These low systemic levels of spectinomycin may contribute to the reduction of *E. coli* within the respiratory tract, however they also bear the risk of underdosing and encouraging antimicrobial resistance (please note that aminoglycosides like spectinomycin are concentration dependent antimicrobials).

To explain this discrepancy in their findings, Goren *et al*., 1988 suggested that a metabolite or degradation product of spectinomycin might reach the respiratory tract and interfere with bacterial attachment. This theory is at best speculative, since it has not been shown that the spectinomycin undergoes any metabolism in any species. For example, in humans all of the injected dose is recovered in urine within 48 hours. In swine, it is excreted unchanged in the urine following intramuscular administration (Cuerpo L, Livingston RC. Spectinomycin. In: Residues of some veterinary drugs in animals and foods. Monographs prepared by the forty-second meeting of the joint FAO/WHO expert committee on food additives. FAO Food Nutr Pap 1994; 41(6): 1-86). This further suggests that if any metabolism of spectinomycin occurs then it would be within the gastrointestinal tract. This is also difficult to believe since studies in other species have concluded that most of the therapeutic dose can be recovered from faeces and urine.

Also, these arguments are further problematic for indications involving *M. gallispeticum*. It is clear that lincomycin is absorbed from the gastrointestinal tract and can have direct clinical effects against *Mycoplasma spp*. However, there is no credible evidence that spectinomycin, at the dose specified on the SPC currently, will have any ‘added value’ on *Mycoplasma gallisepticum*. There are no agreed international standards for MIC determination of *Mycoplasma spp*. Thus, it is difficult to conclude on MIC aspects in support of the combination of lincomycin and spectinomycin on *Mycoplasma gallisepticum*. In addition, spectinomycin is a polar molecule and does not readily cross membranes and distribute into the intracellular compartment. In the recent clinical trial presented in this Article 35 procedure that demonstrated efficacy of oral lincomycin/spectinomycin in chickens experimentally infected with *Mycoplasma gallisepticum*, compared to a placebo control - a lincomycin-only treated group or other monotherapy group was not included in the trial and thus it cannot be determined if the true therapeutic effect was the lincomycin-alone or any added benefit of spectinomycin in the combination of lincomycin/spectinomycin.

Spectinomycin is an aminocyclitol aminoglycoside antibiotic derived from *Streptomyces spectabilis* with bacteriostatic activity. Spectinomycin binds to the bacterial 30S ribosomal subunit. It is used in human medicine for the treatment of gonorrhea infections. Spectinomycin is on the World Health Organization’s List of Essential Medicines, the most important medications needed in a basic health system. More recently the Antimicrobial Advice ad hoc Expert Group (AMEG) has agreed to categorize aminoglycosides used in veterinary medicine as Category 2 (*Antimicrobials used in veterinary medicine where the risk for public health is currently estimated as higher*). Resistance to streptomycin and spectinomycin for example is distinct from resistance to gentamicin, kanamycin and/or tobramycin (Schwarz, S., P. Silley, S. Simjee, N. Woodford, E. van Duijkeren, A.P. Johnson, and W. Gaastra. 2010. Editorial: assessing the antimicrobial susceptibility of bacteria obtained from animals. *Journal of antimicrobial chemotherapy* dkq037.). The most common mechanism of resistance to aminoglycosides in clinical isolates is the production of aminoglycoside modifying enzymes such as acetyltransferases (AAC), nucleotidyltransferases (ANT) and phosphotransferases (APH) (Roberts, M.C., S. Schwarz, and H.J. Aarts. 2012. Erratum: Acquired antibiotic resistance genes: an overview. *Frontiers in microbiology*.). These enzymes modify the aminoglycoside at the hydroxy- or aminogroups of the 2-deoxystreptamine nucleus or the sugar moieties preventing ribosomal binding. To date, there are four acetyltransferases: AAC(1), AAC(2′), AAC(3), and AAC(6′); five nucleotidyltransferases: ANT(2′), ANT(3′), ANT(4′), ANT(6), and ANT(9); and seven phosphotransferases: APH(2′), APH(3′), APH(3″), APH(4), APH(6), APH(7″), and APH(9) (Roberts *et al*., 2012). Although spectinomycin is not a critically important antibiotic for humans (according to the WHO), it can give cross-resistance to streptomycin (which is critically important) via adenyl-
This type of mutation is present in many gram-negative bacteria, also on plasmids (Sandvang et al, Novel Streptomycin and Spectinomycin Resistance Gene as a Gene Cassette within a Class 1 Integron Isolated from *Escherichia coli*. Antimicrobial agents and chemotherapy 1999: 3036). APH(9) and ANT(9) enzymes can also confer resistance to spectinomycin.

In conclusion, low-to-very-low systemic levels of spectinomycin in broilers have led to an unproven hypothesis that it may either be effective against mild airway infections, in combination with lincomycin, or a postulated indirect effect via reduced environment shedding of *E. coli* (as suggested in the rapporteur’s assessment report). The undersigned further highlight other major concerns about the use of spectinomycin in chickens for the respiratory indications described in lincomycin-spectinomycin combination veterinary medicinal products, including:

- The $C_{\text{max}}$ of spectinomycin vs. the MIC has not been determined in broilers.
- There is a risk of underdosing and hence a risk for the selection of resistant bacteria, including cross-resistance to critically important antimicrobials.

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