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OUR REFERENCE [redacted]

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Mr. G. Johan Schefferlie
European Medicines Agency –
Committee for Veterinary Medicinal Products
Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Cc: CVMP members, [redacted]

Via e-mail only

Request for a CVMP scientific advice under Article 141(1)(i) of Regulation (EU) 2019/6 concerning quarter-based selective dry cow therapy

Dear Dr Schefferlie,

Combatting antimicrobial resistance (AMR) is a high priority for the European Medicines Agency (EMA) and the European medicines regulatory network, as recently reflected in the EMANS to 2028. As an integral part of this effort, the European Commission is taking action to contribute to the aspirational target of reducing overall European Union sales of antibiotics for farmed animals and in aquaculture by 50% between 2018 and 2030.[1] The first success of this strategy has already been documented in the latest JIACRA Report[2], which showed that, in countries with decreased consumption of antibiotics in both animals and humans, a reduction in antibiotic-resistant bacteria could be observed.

In this regard, the German Ministry of Food and Agriculture funded the national study "MinimA" (sustained minimisation of antibiotic use through quarter-based selective dry cow therapy in dairy cows) to investigate the potential for reducing antibiotic use by selectively drying-off individual udder quarters in dairy cows. This approach is based on the observation that, in many cases, only one or two udder quarters of a cow are infected before drying off[3]. Thus, individually treating only subclinically infected mastitis quarters with antibiotics at drying-off might result in a significant reduction in overall antibiotic use. The potential for this approach was already shown in various studies[4-7]. The outcomes of the abovementioned German national study indicate such benefits of a selective drying off of individual udder quarters compared to selective dry cow treatment[8,9]. However, the impact of reduction in antibiotic use on AMR was not investigated in the German national study, and the data base regarding this question in connection with antibiotic dry cow therapy seems to be limited. Nonetheless, some data indicate that use of antibiotics at drying off increases antibiotic resistance in mastitis pathogens[10]. There is even some evidence in recent literature that antibiotic use during drying-off in dairy cows

might promote development of resistance in intestinal bacteria and facilitate shedding of resistant strains[11]. It is generally acknowledged that reducing antibiotic use decreases selection pressure for resistance.

According to Article 106(1) of Regulation (EU) 2019/6, veterinary medicinal products (VMPs) shall only be used in accordance with the terms of the marketing authorisation (MA). In Germany, the product information (Summary of Product Characteristics, package leaflet and labelling) for some antimicrobial VMPs authorised for intramammary use at drying-off requires the administration to all four quarters, without distinguishing healthy from infected ones. Moreover, the product information (PI) of some VMPs is often ambiguous regarding whether the VMP should be administered to all four quarters. For instance, in some Summary of Product Characteristics (SPCs) where the indication is for treatment of subclinical mastitis at drying-off, SPC section 3.9 (section 4.9 of the old QRD template) on *'Administration routes and dosage'* does not clearly specify whether only the infected quarters or all quarters should be treated. Furthermore, this lack of clarity extends throughout the SPC, where discrepancies can even arise between the SPC section 3.2 (section 4.2 of the old QRD template) on *'Indications for use for each target species'* and SPC section 3.9. Given that most MAs are valid in several Member States (MSs), this is most likely to be the case in those MSs as well. Consequently, the authorised wording in the PI of certain antibiotic VMPs intended for use at drying off prevents veterinarians and farmers from practicing quarter-based selective drying off, if the content of the PI does not explicitly support this practice.

In the context of prudent use of antibiotics, Germany considers it necessary to review whether it is scientifically justifiable to generally allow quarter-based selective dry cow therapy with antibiotic udder VMPs. Such an approach would allow veterinarians to decide in appropriate cases on a quarter-based selective dry cow therapy in accordance with the terms of the marketing authorisation, thereby reducing antibiotic use and lowering the risk of resistance development.

In view of the elements described above, Germany considers it necessary to request the Committee for Veterinary Medicinal Products (CVMP) to provide scientific advice under Article 141(1)(i) of Regulation (EU) 2019/6 on whether the PI of intramammary antibiotic VMPs used at drying off should be amended to allow for (not exclude) selective treatment at quarter level, without contradicting national policies.

The CVMP is requested to provide scientific advice on the following aspects:

- Considering all available scientific data, the CVMP is asked to assess whether quarter-based selective dry cow antibiotic therapy could be considered consistent with the latest scientific knowledge aimed at reducing antibiotic use, without compromising animal health.
- If quarter-based selective dry cow therapy is deemed an effective strategy to reduce antibiotic use, the CVMP is asked to advise on how this approach could be reflected in the PI of the relevant intramammary antibiotic VMPs. This would enable veterinarians and farmers to practice quarter-based selective dry cow therapy in accordance with the terms of the marketing authorisation.

In relation to the request above, the CVMP is asked to collect all available data to support the scientific advice on the subject.

Yours sincerely,

[redacted]

On behalf of Prof. Heberer

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