Veterinary antibiotic availability: what the future holds

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Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (OJ L 004, 9.01.2019, p. 43) or more succinctly, Regulation 2019/6, was applied throughout the European Union from January 2022. One of its key aims is to address the public health risk of antimicrobial resistance (AMR). Acknowledging the 'one health' dimension to AMR, the Regulation itself contained a number of measures to address AMR that are targeted exclusively at the authorisation, use and monitoring of veterinary medicines. The legislative measures include requiring that all antimicrobials (including anti-fungals and anti-protozoals) be subject to veterinary prescription control. It also provides for a number of other measures, including secondary regulations governing, e.g., exclusive restriction for certain antibiotics used in humans, regulations governing the cascade use of veterinary antibiotics etc. Significantly, in an effort to preserve the efficacy of older antibiotics, the Regulation also introduced requirements for changes to the instructions for use of veterinary antibiotics, while mandating the review of older antibiotics. Such reviews carry downside risks in addition to their intended goal of improving product efficacy and minimising the potential for resistance to develop.

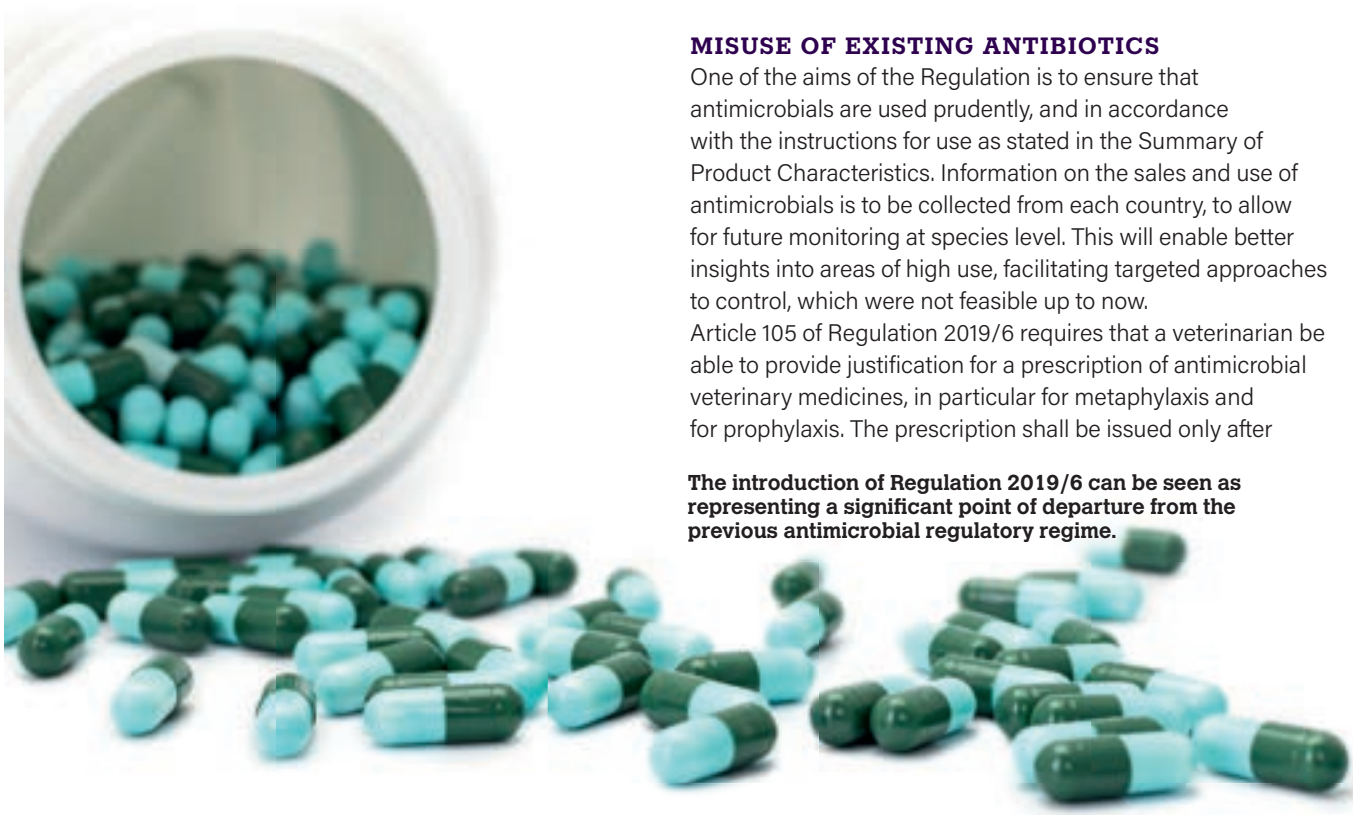
DEVELOPMENTS IN RELATION TO NEW ANTIBIOTICS

Even though the Regulation provides additional data exclusivity incentives for the development of new antibiotics or for the improvement of the resistance profile of established compounds, the technical requirements that must be fulfilled before a marketing authorisation can be granted have increased, compared to previous requirements. In particular, information on the potential for development of resistance in humans must be provided. Moreover, the development of resistance in non-target bacteria in animals must also be investigated. Finally, the envisaged indication for use must be carefully crafted and proven, the goal being to ensure that the use of the new antibiotic is safeguarded and limited to those situations where other antibiotics have been shown not to be useful. In the face of the data required and the restricted market for the eventual indication for use, marketing authorisation holders have not surprisingly shown little appetite to develop new antibiotics for veterinary use. Furthermore, new combinations of different antibiotics are considered to present a particular risk with respect to the development of resistance and are also unlikely to be authorised.

MISUSE OF EXISTING ANTIBIOTICS

One of the aims of the Regulation is to ensure that antimicrobials are used prudently, and in accordance with the instructions for use as stated in the Summary of Product Characteristics. Information on the sales and use of antimicrobials is to be collected from each country, to allow for future monitoring at species level. This will enable better insights into areas of high use, facilitating targeted approaches to control, which were not feasible up to now.

Article 105 of Regulation 2019/6 requires that a veterinarian be able to provide justification for a prescription of antimicrobial veterinary medicines, in particular for metaphylaxis and for prophylaxis. The prescription shall be issued only after



The introduction of Regulation 2019/6 can be seen as representing a significant point of departure from the previous antimicrobial regulatory regime.

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a clinical examination or other proper assessment of the health status of the animal or animals. The prescription for antimicrobials is valid only for five days from the date of issue. These measures are expected to limit the potential for any misuse.

Article 106 of the Regulation requires that veterinary antibiotics be used according to the Summary of Product Characteristics (SPC) and that any misuse should not be allowed. It should be noted that, by way of derogation from this article, it is allowed to use certain antimicrobials under the cascade provisions (cascade provisions refer to legal provisions that allow a veterinarian to prescribe a medicine in situations where there is not authorised veterinary medicine for the condition or animal requiring treatment). The European Medicines Agency (EMA) is currently working to provide the EU Commission with scientific advice on which antimicrobials can be used under the 'cascade' and under what conditions, as well as which antimicrobials will not be allowed to be used. The Commission is expected to elaborate the relevant secondary Regulation before the end of 2022.

According to the Regulation, the amounts of veterinary medicines prescribed or supplied by veterinarians should be restricted to the amount required for treatment of the animals under her/his care. Furthermore, in the case of antimicrobials for metaphylaxis or prophylaxis, they can be prescribed only for a limited duration to cover the risk period.

KNOWN REGULATORY CHANGES TO PRODUCT LABELLING

Actions that must be implemented over the next year or so include:

- Removing any indication for prophylactic use of antibiotics from the labelling and package information, except where such use can, in exceptional circumstances, be justified. This work is expected to get underway in earnest early in 2023, following the adoption of an EMA reflection paper on prophylactic use of antimicrobials in animals[1] in the context of Article 107(3) of Regulation (EU) 2019/6 by December 2022. This document was recently published for public consultation and, while the consultation is closed, a draft of the reflection paper can be found on the EMA website.
- Ensuring that any indication for metaphylactic use is appropriate and where no appropriate alternatives are available.
- Strengthening prudent use warnings where necessary.

Among the planned regulatory changes to the labelling of veterinary medicines over the coming two to three years is better precision for the instructions for use of veterinary medicines which are administered orally in feed or drinking water. The goal is to ensure proper administration and avoid cross-contamination.

CHANGES TO EXISTING ANTIBIOTICS

Building on an earlier pilot methodology for dose optimisation, and in the knowledge that some older antibiotics are used in clinical practice at dosages that are higher than those stated on the SPC and label, the EMA is exploring the possibility of using novel approaches to extrapolate scientific data on older antimicrobials to see if such data can yield more effective dosage recommendations, without having to require new experimental animal studies. The pilot study[2], which was conducted using oral amoxicillin in pigs and oxytetracyline injection in cattle showed that it can be possible to use PK/PD data as well as published literature to derive new dosage recommendations, without the need for new target animal efficacy and safety studies.

Once the EMA agrees a priority list of candidate antibiotics for review of their dosage later this year, the work on dose optimisation will begin. A complicating factor in this work is that a complete data set to allow the model to function properly might not be available for all antimicrobials, or for all species. A further issue is that the higher the dosage that might be judged optimal for the control of a pathogen, the greater the quantity of antibiotic that is available to promote resistance in non-target bacteria, whether in the animal's own body or in the environment.

Over the period to 2025, the EMA is expected to review the instructions for use of veterinary medicinal products containing macrolides as well as those containing lincosamides. Recognising their importance as critically important antimicrobials (CIAs) or highly important (HI) respectively in human medicine, the goal here is to review and adapt dosing regimens and indications. The EMA has previous experience of reviewing certain veterinary medicines containing tylosin, lincomycin, and lincomycin/spiramycin. That led to the removal of indications against swine dysentery caused by *B. hyodysenteriae* from the products concerned.

In February 2022, the EMA commenced a review of veterinary medicines containing procaine benzylpenicillin presented as suspensions for injection, following a referral by Germany. The issue is that dosages of existing products vary significantly, and they might not be appropriate to treat all claimed indications effectively, risking the development of resistance. The procedure includes veterinary medicines for use in cattle, horses, sheep, goats, pigs, dogs and cats. The review is ongoing and is expected to conclude early in 2023.

PREVIOUS CASE STUDIES

Whilst past experience is not always predictive, it is worth considering three case studies which demonstrate how the

regulatory network addressed antibiotic reviews under similar circumstances.

Doxycyline 50% powder for use in drinking water and used for treatment of poultry, pigs and pre-ruminant calves

This referral procedure[3] dates from 2010 and was undertaken to harmonise the indications, target species, dosage and withdrawal period for similar products licensed in 10 Member States (MS), having been initiated by the United Kingdom. The dosages in the EU varied from 25-40mg/kg for three to seven days in poultry, 10-20mg/kg for three to five days in calves and 10-20mg/kg for three to seven days in pigs. Following the one-year procedure, the EMA concluded:

- In the absence of data from species of poultry other than chickens, the indication should be restricted to chickens. The indications for treatment of *E.coli* should be based on the results of susceptibility testing, but a dosage of 25mg/kg for five days was supported.
- For pigs, although the data suggested that a dose of 10mg/kg for three to five days might not be optimal, there was no clear evidence on which to base a revision of the dose/indications. The available residue data supported a meat withdrawal period of eight days at a dose of 10mg/kg for five days.
- For calves, the available data did not support all indications for use, and therefore some alterations in the indications were made. However, there was sufficient evidence to support a dosage of 5mg/kg given twice a day for five days.

Enrofloxacin for use in drinking water to chickens and turkeys

This referral procedure[4] dates originally from 2012, and followed an earlier referral to improve the prudent use warnings for fluoroquinolones. The issue under consideration was the dosage regimens needed to ensure optimal efficacy and to reduce selection of resistance. There were over 200 separate products involved in almost all MSs. The companies involved were requested to provide data justifying the dosage of enrofloxacin in poultry by February 2017. Subsequently, the EMA reviewed the available pre-clinical and clinical which was provided, as well as published literature. The outcome was that the available data was insufficient to support a claim for treatment of infections caused by *E. coli* in chickens and turkeys; therefore, the indication had to be removed from the SPC and labelling.

Paromomycin for use parenterally to pigs

In 2018, Belgium referred this issue[5] to the EMA on the basis that there were differences in indications, dosages, and withdrawal periods for similar products in the EU. Following consideration of the available evidence, the EMA concluded that the efficacy of the medicines was not supported for any indication or dosage, and could pose a risk of resistance development. The EMA considered that the 21 veterinary medicines on the market in the EU should be suspended, pending the availability of the new studies requested, as well as an updated benefit-risk assessment. That recommendation was confirmed by the EU Commission in October 2019.

One of the aims of Regulation 2019/6 is to ensure that antimicrobials are used prudently.

CONCLUSION

The application of Regulation 2019/6 in January 2022 can be seen as a point of departure from the previous regulatory regime for antimicrobials. Not only are there new legal controls in place to limit the potential for misuse of antimicrobials, but veterinarians are given a pivotal position to apply their knowledge, training and professional judgement to ensure their prudent use. Moreover, the professional standing of veterinarians is recognised in the Regulation, and all are expected to show leadership in the period ahead.

In addition to the legal controls on veterinary antimicrobials, the regulatory controls on them also continue to tighten. This is necessary in order to maintain their effectiveness while minimising their potential to induce resistance. In some cases, new data on their efficacy will be available that will force the EMA to question the evidential basis for existing indications. The forthcoming reviews to optimise the dosage and indications will not be limited only to CIAs, but will embrace older antibiotics.

REFERENCES

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4. Veterinary medicines containing enrofloxacin to be administered via the drinking water to chickens and/or turkeys, European Medicines Agency (europa.eu).
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