New veterinary legislation and off-label use: the devil is in the details

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Today, veterinary medicines and medicated feed in EU are regulated by mainly 2 regulations. The first one is regulation 2019/6 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006) , setting the regulatory framework for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, control and the use of veterinary medicinal products. The second one is regulation 2019/4 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0004) , setting the regulatory framework for the preparation, placing on the market and use of medicated feed. Medicated feed is one of the routes for the oral administration of veterinary medicinal products, but as such not considered as a veterinary medicine anymore. This is why there is a different regulation for medicated feed. In this article, some specific parts of the regulations, that are important on a daily base for the veterinary practitioner.

Regarding regulation on medicated feed:

1. A veterinary prescription for medicated feed shall be issued only after a clinical examination or any other proper assessment of the health status of the animal or group of animals by a veterinarian and only for a diagnosed disease. However, if it is not possible to confirm the presence of a parasitic infection, a veterinary prescription for medicated feed containing anti-parasitics without antimicrobial effects may be issued based on the knowledge of the parasite infestation status in the animal or group of animals (article 4).

2. In the original regulation, no maximum allowed carry-over level was set. This has now been established by a delegated act at a maximum carry over level at 1%. (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L_202401229)

3. Medicated feed containing antimicrobial veterinary medicinal products shall be used in accordance with Article 107 of Regulation (EU) 2019/6, meaning for example that the same rules on off-label use for veterinary products also apply for medicated feed.

Regarding regulation on veterinary medicines:

- Off-label use (or extra-label as it named in US)
  In the case of food-producing terrestrial species if there is no authorised medicine OR the product(s) are not available on the market, to treat a condition, a veterinarian may administer/ prescribe, to avoid causing unacceptable suffering, medicinal products outside the terms of the marketing authorisation or SPC. There are different options, but for food-producing animals, only below options are being used in practice:
  "*a veterinary medicinal product authorised in the Member State or in another Member State for use in the same or in another food-producing terrestrial animal species for the same indication, or for another indication.*"
  Important to note, is that a practitioner can chose between options above, and it is no longer necessary to first select for example a product in the same member state for the same species. Also a combination is possible, like a product from another member state for another species with another indication.
  If above is not possible, products can also be used in following descending order of suitability (or also called cascade system):

- relevant Member State for use in a non-food-producing animal species for the same indication
- a medicinal product for human use
- a veterinary medicinal product prepared ex-temporaneously
- veterinary medicine authorised in a third country (e.g., UK) for the same species and same indication (not for immunological products)

Most important is to realise that, in all cases of off-label use, the prescribing veterinarian is responsible for all possible adverse events (safety, efficacy,...) that can happen.

Important to note, is that Regulation (EC) No 470/2009 always stays valid. It means basically, if a veterinary product is used for which no maximum residue level (MRL) is established, any residue found in foodstuff, can be considered as a non-allowed substance with severe consequences, for the veterinary practitioner, who is responsible for all risks related to off-label use. Regulation clearly states only pharmacological substances with a species specific MRL, a provisional species specific MRL absence of the need to establish MRL can be administered (article 16 in accordance with article 14(2)a, b, c and can the foodstuff can be placed on the market.(article 23)

So, the advice could be to only prescribe off-label if a MRL is available for the concerned species. Luckily for the poultry sector, most MRL's are set as poultry (or all food producing species), what also includes turkeys.

The list can be found in this link:
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:015:0001:0072:en:PDF

Setting withdrawal time in case of off-label use is straight forward:

For meat and offal from food-producing mammals and poultry and farmed game birds the withdrawal period shall not be less than:

(i) the longest withdrawal period provided in its summary of the product characteristics for meat and offal multiplied by factor 1,5;
(ii) 28 days if the medicinal product is not authorised for food-producing animals;
(iii) one day, if the medicinal product has a zero withdrawal period and is used in a different taxonomic family than the target species authorised; turkeys fall under the same taxonomic family as chickens.

If a product is used off-label for a non-registered indication but for the same species, at the registered dose, the withdrawal time remains as it is on the label.

There are some exceptions concerning antibiotics.
(https://www.ema.europa.eu/system/files/documents/regulatory-proceduralguideline/vet_reg_cascade_list_report_en.pdf)

Some examples:

- Amoxicillin-clavulanic acid cannot be used in poultry.
- Florfenicol, 3rd and 4th generation cephalosporines,quinolones and fluoroquinoles can only be used after an antibiogram has been performed and no antibiotic can be used that has lower AMEG classification.
- Some products cannot be used to treat Salmonella for group treatment, like fluoroquinolones and 3rd and 4th generation cephalosporines

Finally, there is also a new delegated regulation regarding the effective and safe use of veterinary medicinal products authorised and prescribed for oral administration via routes other than medicated feed and administered by the animal keeper to food-producing animals. Several points are discussed, like the use of so-called oral granules for individual use. More relevant for the poultry industry, are Biocidal products, feed additives or other substances used in drinking water. They shall not be used simultaneously with a veterinary medicinal product where there is evidence of negative interactions or incompatibilities between those products and the veterinary medicinal product when added to drinking water.

(https://eur-lex.europa.eu/legalcontent/EN/TXT/PDF/?uri=OJ:L_202401159)

GB legislation is a bit different than EU legislation regarding off-label use:

Where there is no suitable veterinary medicine authorised in your territory for the specific condition in the animal being treated, to avoid unacceptable suffering, you are permitted to use your clinical judgement to treat animals under your care in accordance with the cascade.

The steps, in descending order of suitability, are:

- Veterinary medicine with a Marketing Authorisation valid in GB or UK wide for indicated species and condition
- Veterinary medicine with a Marketing Authorisation valid in NI for indicated species and condition, in accordance with a Special Import Certificate granted by the VMD
- Veterinary medicine with a Marketing Authorisation valid in GB, NI or UK wide for a different species or condition. For products not authorised in GB or UK wide a Special Import Certificate from the VMD is required

All substances contained in the medicine must be substances which have a Maximum Residue Limit (MRL), but not necessarily in the species for which it is intended to be used! **This is different from EU legislation!**

The vet responsible for prescribing the medicine must specify an appropriate withdrawal period

- the longest withdrawal period provided in the SPC for meat and offal, multiplied by a factor of 1.5
- 28 days, if the product is not authorised for food-producing animals
- 1 day, if the product has a zeroday withdrawal period