The New Veterinary Regulation – key changes

Under the New Veterinary Regulation, certain professional and ethical prescribing liberties that attached to veterinarians under the existing legislation are expected to be significantly curtailed. This applies in particular to the future use of antibiotics and especially to the use of critically important antibiotics for humans in animals.

Dr J. G. Beechinor MVB, MVM, MSc, PhD, CDipAF, MRCVS, Director of Veterinary Sciences, Health Products Regulatory Authority, outlines the main changes affecting veterinary practitioners and nurses that will arise in relation to Regulation 2019/6, the so-called New Veterinary Regulation (NVR). Dr Beechinor is a member of the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency (EMA)

Regulation 2019/6 (so-called New Veterinary Regulation [NVR]), regulates how veterinary medicinal products are authorised, used and monitored in the European Union (EU). It applies from 28 January, 2022. The NVR also establishes a new, centralised, database of all EU authorised medicines (whether authorised centrally or in Member States). Furthermore, it establishes new systems for monitoring adverse reactions to veterinary medicines, allowing for real-time monitoring of reports and better compliance tools.
In Ireland and other Member States, the NVR will be complemented by secondary EU legislation as well as new national legislation. The secondary EU legislation takes the form of delegated and implementing acts. There are more than 25 such acts, which establish more granular details about e.g., technical requirements for application dossiers, restrictions on the use of antibiotics in veterinary practice and the operation of the 'cascade' rules governing off-label use of medicines. About half of them will be established by the date of application, with the remaining acts being elaborated in the future, as society develops. The national legislation will give effect to certain legal choices in specific areas that are provided in the NVR, e.g., whether certain medicines for specific pet species or aquarium fish are to be exempted from the requirement for marketing authorisation or not. In Ireland, some provisions of the existing national legislation conflict with the requirements of the NVR (e.g., the highest form of control in the method of supply of new medicines is under veterinary prescription rather than VPO as specified currently) and, therefore, there is a need to update the national legislation in any event.

This article will deal with the main changes that arise in relation to the NVR. The Department of Agriculture, Food and the Marine (DAFM) is responsible for elaborating changes to the national legislation; that legislation is not expected to be available until year-end or in early 2022.

OBJECTIVE

The revision of the legislation has a number of objectives:

1. To decouple the EU veterinary legislative framework from that relating to human medicines, so that the requirements for veterinary medicines are fit for purpose. The existing legislation borrowed heavily from that of human medicines but the resources available for monitoring human medicines are vastly greater. Moreover, human medicines are often funded by public taxes, whereas veterinary medicines will only be developed where there is a commercial return.
2. To safeguard public and animal health, as well as food safety and protection of the environment. The underpinning quality, safety and efficacy standards have served citizens well and will be maintained under the NVR.
3. To reduce administrative burden and foster innovation. The bureaucracy associated with maintaining the current regulatory requirements was seen as being disproportionate for animal health companies, compared to the human pharmaceutical sector. Moreover, additional incentives to foster innovation and development of existing veterinary medicines were needed, especially given the lack of medicines for minor use and minor species (MUMS).

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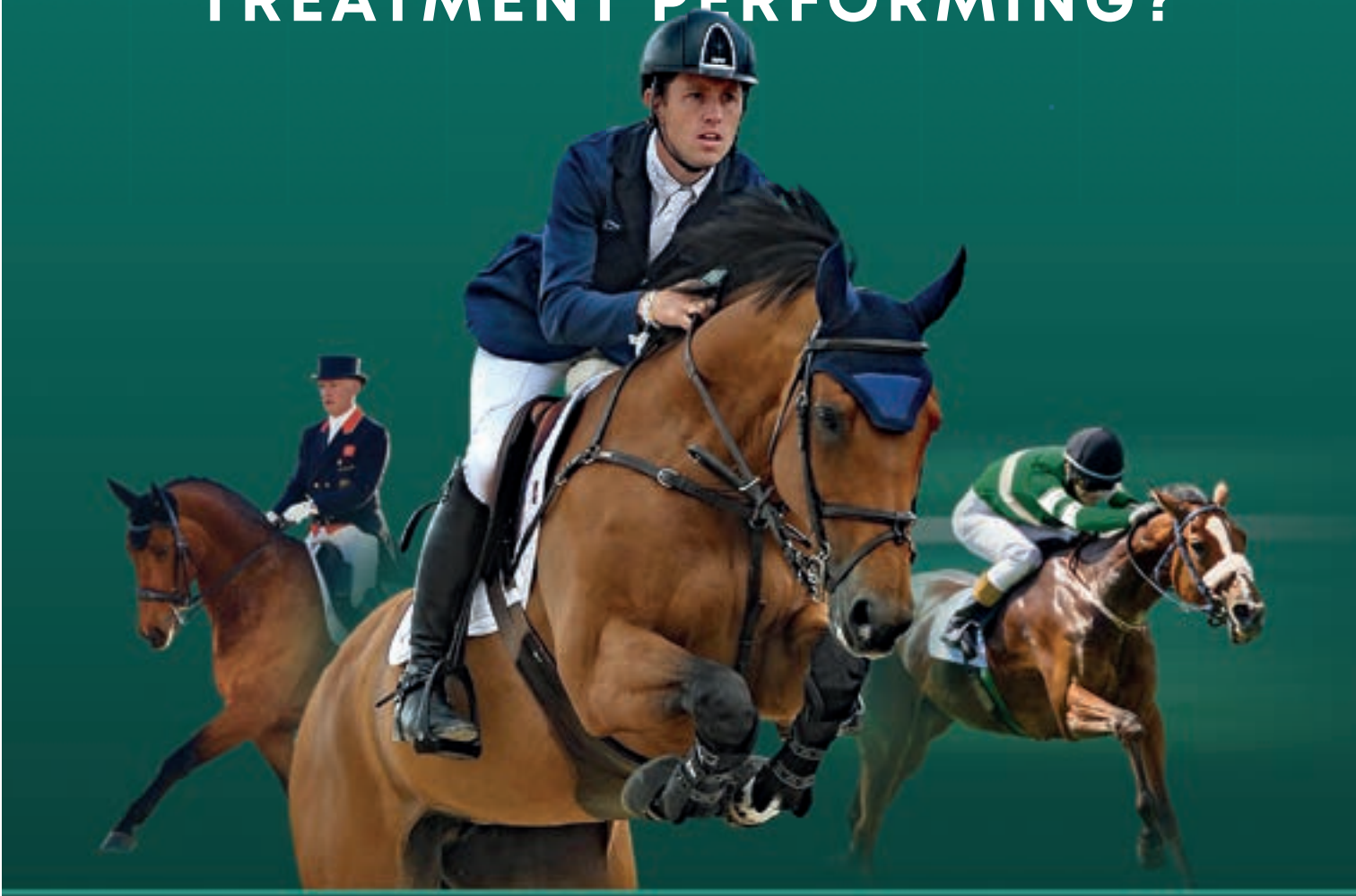

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References: 1. Sykes BW, et al. ECEIM Consensus Statement – EGUS in Adult Horses. J Vet Intern Med 2015; 29: 1288-1299.

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In Ireland and other Member States, the NVR will be complemented by secondary EU legislation as well as new national legislation.

4. To improve availability of veterinary medicines in the EU, including the functioning of the internal market. Many veterinary medicines are authorised for only a few national markets, which are small and fragmented compared to human medicines. Streamlining of labelling requirements could revolutionise this dilemma, by facilitating multilingual product labels.
5. To tackle antimicrobial resistance (AMR). AMR is a significant problem for human health in particular. It is linked closely to antibiotic consumption. Veterinary antibiotic use is viewed to contribute to resistance in humans, even if the relationship is sometimes unclear and contested.

SIGNIFICANT CHANGES

While there are many changes to the authorisation systems and processes, only those changes that affect veterinary practitioners and nurses are discussed here. For a complete interpretation, the reader is invited to consult the regulation itself.

Availability of information on authorised veterinary medicines

When available in 2022, the Union Product Database (UPD) will contain information on all veterinary medicines that are authorised in the EU. This will be a significant step in improving transparency in respect of veterinary medicines in the EU, as it is expected to provide information eventually on more than 30,000 individual medicines, once national product information is uploaded by Member States. The database, which will be housed by the European Medicines Agency (EMA), will include extensive and searchable information on medicines, including summaries of product characteristics (SPCs) and package leaflets.

Pharmacovigilance surveillance

Marketing authorisation holders (MAHs) will be required to monitor adverse reactions and to analyse their frequency, to detect for possible signals for a change in the benefit risk profile of their medicines. The outcome of the analysis must be recorded in the EMA's Union Pharmacovigilance Database, which will be linked to the UPD. While the process for notifying MAHs and national regulatory authorities of suspected adverse reactions will remain as it is today, the change in the analytical methodology is expected to result in faster regulatory responses (e.g., updating of product information with new safety warnings). A feature of the surveillance is that there will no longer be a causality assessment needed before upload of a report to the database,

Under current national legislation, the HPRA could exempt certain antiparasitic and antifungal medicines (oral and topical presentations) that were indicated for aquarium and pond animals, from the requirements for a marketing authorisation. Under Regulation 2019/6, such products must either be registered or authorised by the HPRA.

The precise changes affecting veterinary antibiotics are being elaborated under EU secondary legislation currently; the aim is to restrict certain categories of antibiotics that are deemed critical for humans, and to ban preventative use in groups of animals.

meaning that reporting of spurious reactions is possible. This development could lead to web-savvy owners unearthing unproven or dubious side effects, as the pharmacovigilance database will be searchable by the public.

Labelling of medicines

The labelling of the immediate packaging of veterinary medicines is set to be rationalised in order to facilitate the development of multilingual products. From January 2022, information on the indication for use, dosage, method of supply and marketing authorisation number will no longer appear on the immediate labels of new medicines. Once EU secondary legislation on the use of pictograms (icons) is agreed within the next few years, the target species will be replaced by appropriate icons on the product labelling. Changes will also be made to the outer packaging, which will be similarly truncated, but will contain warnings that:

- the product is for animal treatment only;
- the product must be kept out of sight and reach of children; and
- the user should read the package leaflet.

The outer pack will also contain the marketing authorisation number, although even this identifier may be replaced by a 'code' if agreed in secondary EU legislation over the coming years. In the case of medicines that are not subject to veterinary prescription, the outer pack must also list the indications for use. In any case, all relevant information, including the method of supply, must instead be contained in the package leaflet, which might be made available electronically in addition to paper copy.

Registration of medicines for certain pets and aquarium fish

Under current national legislation, the HPRA could exempt certain antiparasitic and antifungal medicines (oral and topical presentations) that were indicated for aquarium and pond animals, cage birds, homing pigeons, terrarium animals, small rodents, ferrets and pet rabbits from the requirements for a marketing authorisation. Under Regulation 2019/6, the regulatory position has been tightened, and this will mean that, from 2022, such products must either be registered or authorised by the HPRA. While the authorisation requirements of quality, safety and efficacy are the same as for other medicines, the registration requirements are somewhat lighter (e.g., limited safety and efficacy studies are needed, but full quality and pharmacovigilance requirements apply).

Changes to the cascade

The underlying principle that a veterinarian can treat an animal with an unauthorised medicine, exceptionally, to avoid causing unacceptable suffering to an animal will remain. However, certain provisions have been changed in the NVR. In the case of non-food-producing animal species, if there is no authorised medicine to treat a condition, a veterinarian may administer to an animal:

(a) A veterinary medicine authorised in Ireland or another EU Member State for use in the same species or in another species;
(b) If there is no authorised medicine available under (a), a medicine authorised for human use in the European Union;
(c) If there is no authorised medicine available under (a) or (b), a veterinary medicine that is prepared extemporaneously in accordance with a veterinary prescription.

If there is no authorised medicine available under (a) or (b) and no product available under (c), a vet may use a veterinary medicine authorised in a third country (e.g., UK) for the same species and same indication. This last provision does not apply to immunological products.

In the case of food-producing terrestrial species if there is no authorised medicine to treat a condition, a veterinarian may administer to an animal:

(a) A veterinary medicine authorised in Ireland or another EU Member State for use in the same species or in another food-producing species;
(b) If there is no authorised medicine available under (a), a veterinary medicine authorised in Ireland for use in a non-food animal species for the same indication;
(c) If there is no authorised medicine available under (a) or (b), a medicine authorised for human use in the European Union;
(d) If there is no authorised medicine available under (a), (b) or (c), a veterinary medicine that is prepared extemporaneously in accordance with a veterinary prescription;
(e) If there is no authorised medicine available under (a), (b) or (c) and no product available under (d), a veterinary medicine authorised in a third country (e.g., UK) for the same species and same indication. This provision does not apply to immunological products.

In all the above cases, the substances used in the medicine must comply with the legislation on maximum residue levels (Regulation 470/2009). However, the essential substances list for horses can continue to be used in the same way as under current legislation, with a withdrawal period of six months; the list will be updated by 28 January, 2027. Similar provisions apply to the use of medicines in food-producing aquatic species, save that there will be new secondary EU legislation to establish an EU list of substances for use in aquatic species before 28 January, 2027.

There are significant changes to the withdrawal periods needed for medicines used off-label in the new regulation. The withdrawal for meat and offal will be not less than:

(i) The longest withdrawal period given for meat and offal for any species multiplied by a factor of 1.5;

(ii) 28 days, if the medicine is not authorised for food-producing animals;
(iii) One day, if the medicine has a zero withdrawal period for another target species.

The withdrawal period for milk shall be not less than:
(i) The longest withdrawal period given for milk multiplied by a factor of 1.5;
(ii) Seven days, if the medicine is not authorised for milk producing animals;
(iii) One day, if the medicine has a zero withdrawal period.

The withdrawal period for eggs shall be not less than:
(i) The longest withdrawal period given for eggs multiplied by a factor of 1.5;
(ii) 10 days, if the medicine is not authorised for egg producing birds.

The withdrawal period for aquatic species shall be not less than:
(i) The longest withdrawal period given for any aquatic species multiplied by a factor of 1.5 and expressed as degree-days;
(ii) If the medicine is authorised for food-producing terrestrial species, the longest withdrawal period multiplied by a factor of 50 and expressed as degree-days, but not exceeding 500 degree-days;
(iii) 500 degree-days, if the medicine is not authorised for food-producing animals;
(iiii) 25 degree-days, if the longest withdrawal period for any animal species is zero.

Where the calculated withdrawal period results in a fraction of a day, the results shall be rounded up to the nearest number of days.

For bees, the veterinarian shall determine the appropriate withdrawal period for honey on a case-by-case basis taking into account the risk of residues.

Changes to antibiotics

The precise changes affecting veterinary antibiotics are being elaborated under EU secondary legislation currently; the aim is to restrict certain categories of antibiotics that are deemed critical for humans, and to ban preventative use in groups of animals. While the EMA has proposed a nuanced, risk-based approach to restricting certain classes of veterinary antibiotics, in July 2021 the European Parliament adopted a motion opposing the legislation on the basis that it was too lax. The motion called for the banning of all critically-important antibiotics used in human medicines from any use in veterinary (including companion animals), and would have included third and fourth generation cephalosporins, macrolides, aminoglycosides, ampicillin, amoxicillin and fluoroquinolones. The subsequent vote by the European Parliament in September to ensure that veterinarians retain access to life-saving antimicrobial therapy for animals is hugely significant but will delay the finalisation of the antibiotic list until early 2022..

Changes to anti-parasitic medicines for food-producing animals

The HPRA completed the changing of the legal method of supply for antiparasitic veterinary medicinal products for food-producing animals from licensed merchant (LM) to prescription only medicines (POM) at the end of July 2021. However, the associated changes to the product labelling may take a number of months, and similar products displaying either LM or POM may co-exist in retailers until 28 January, 2022. After this deadline, a veterinary prescription will be required. In accordance with the HPRA report, antiparasitic veterinary medicinal products for bees may continue to be marketed without a veterinary prescription, while antiparasitic medicines for dogs and cats are not affected by this development.

TIMELINES

Although the UPD is expected to be available from the date of application of the NVR on 28 January, 2022, it is possible that Member States might not have completed the upload of their national product data for a period of time afterwards.
New medicines that are authorised from 28 January, 2022, will have to comply with the new labelling requirements, but existing medicines do not have to comply until January 2027. However, it is expected that many companies will take the opportunity to simplify the product labelling well in advance of this deadline. The change of labelling to replace text with the use of pictograms and to provide for an EU identification code will require secondary legislation, which will take a few years to elaborate.
Certain changes to the operation of the cascade as they relate to use of antibiotics off-label, which are being elaborated currently in the EU, are expected to become operational in early 2022. The details are not yet finalised, but the expectation is that there will be a more restrictive framework in place. By January 2027 at the latest, the essential list of substances for equine species will be revised and new cascade rules for food-producing aquatic species will be elaborated.

CONCLUSION

While much of the current legal requirements for the authorisation and use of veterinary medicines has been carried forward into the NVR, there are significant changes too. This article has focused on certain changes which are considered most relevant to the veterinary profession, but for definitive interpretation the reader should read the regulation in full.
Even if the NVR is expected to accelerate the development of innovation and medicines for minor species, certain professional and ethical prescribing liberties that attached to veterinarians under the existing legislation are expected to be significantly curtailed. This applies in particular to the future use of antibiotics and especially to the use of critically important antibiotics for humans in animals.
The NVR will be complemented in Ireland by the introduction of new national legislation. The interpretation of certain provisions of the NVR is likely to be affected by this development.