Opening statement of the HPRA to the Joint Committee on Agriculture and the Marine
27 April 2021

I would like to thank the Chairman, TDs and Senators for inviting the Health Products Regulatory Authority (HPRA) to appear before them this evening. I am joined by Dr. David Murphy, a member of the management team in the HPRA's veterinary sciences department, who is currently serving as chairman for the Committee for Medicinal Products for Veterinary Use at the European Medicines Agency (EMA). Dr. Murphy has served the HPRA since 1999, while I myself joined in 1987.

We welcome the opportunity to address the Committee on two topics, namely the new veterinary regulation (Regulation 2019/6) and controls of the sales of animal remedies.

Role of the HPRA
I would first like to clarify the role of the HPRA in the field of veterinary medicinal products (VMPs). Our role is to ensure that medicines are of good quality, and that they are safe and effective. We do this by reviewing applications for marketing authorisation and ensuring that the medicines comply with the regulatory standards in place, as well as relevant European and national legislation. Following the launch of medicines to the marketplace, we review the benefit / risk balance of products on an ongoing basis by means of pharmacovigilance monitoring. I would like to clarify that the Department of Agriculture, Food and the Marine (DAFM) regulate downstream activities relating to the wholesale, retail and use of veterinary medicines. DAFM also legislate nationally in respect of the conditions that must be fulfilled for the prescribing, dispensing, use and disposal of veterinary medicines nationally.

In short, the role of the HPRA extends to evaluating applications for veterinary medicines and vaccines and setting the parameters for their use by issuing marketing authorisations.

The new veterinary regulation
The Committee has already been informed about the objectives of the new veterinary regulation so I will not go into detail again, other than to say that one of the overarching objectives of the legislation is to ensure a high level of protection of animal health, animal welfare and the environment and safeguarding public health.

The new regulation also aims to reduce the administrative burden for the animal health industry and thereby improve availability of medicines. This is to be achieved by, amongst others:

- Simplification of packaging and labelling textual information on medicines, and replacing text with pictograms and abbreviations that are standardised across the Union. Comprehensive instructions for use will instead be placed within the package leaflet, which may be in several Community languages, thereby facilitating the creation of common EU packaging rather than individual national package requirements. The package leaflet may be made available in paper or electronically, or both, being the choice of the Member State.
- The creation of a Union database of authorised veterinary medicines from every EU Member State. This database, which is being developed currently and which will contain information on over 30,000 individual authorised medicines, is to go live on 28 January 2022. This milestone is expected to facilitate the identification of effective medicines from other Member States that will be available to treat animal diseases in this country.
- The creation of a Union database of suspected adverse reactions for all veterinary medicines that are authorised within the Community. This development, which will in time replace current databases held by each competent authority, is expected to improve detection of suspected adverse events and facilitate work-sharing between competent authorities throughout the EU.

Addressing resistance
The new regulation places significant emphasis on addressing resistance, both antimicrobial resistance as well as antiparasitic resistance.

In relation to antimicrobial resistance, the regulation acknowledges that antimicrobial resistance to medicinal products both for human and veterinary use has become a global public health concern that affects the whole of society and requires urgent and coordinated inter-sectoral action in accordance with the 'One Health' approach. Accordingly, the regulation includes provisions aimed at strengthening the prudent use of antimicrobials, avoiding their routine prophylactic use, restricting the use in animals of antimicrobials that are of critical importance for preventing or treating life-threatening infections in humans and encouraging and incentivising the development of new antimicrobials. It is also stated that the rules for the authorisation requirements of antimicrobial VMPs should sufficiently address the risks and benefits of these products and, in particular, an application for an antimicrobial VMP should contain information about the potential risk that use of that medicinal product may lead to the development of antimicrobial resistance in humans or animals or in organisms associated with them. The regulation also recognises that, given the limited innovation in developing new antimicrobials, it is essential that the efficacy of existing antimicrobials be maintained for as long as possible. The legislation therefore seeks to minimise the risk of antimicrobial resistance arising from the use of these products in veterinary medicine.

In relation to antiparasitic substances, which include anticoccidial therapies, anthelmintics, flukicides and ectoparasitic drugs, concern has been raised about an increase in the development of resistance in parasites also. Whilst there is not a direct human health risk of antiparasitic resistance, it has adverse consequences on animal health and welfare, and on farm productivity. The manifestation of resistance in an animal is often insidious in onset, meaning that farmers and animal owners might not be aware that resistance is present until a substantial percentage of the animals are affected. The new regulation states that a marketing authorisation shall be refused if the risk of development of antiparasitic resistance outweighs the benefits of the veterinary medicinal product to animal health. The regulation also provides new regulatory tools to stimulate investment in, and the development of, medicines that address antiparasitic resistance.

The primary role of the HPRA in addressing resistance, be it in respect of antimicrobials or antiparasitics, is to ensure that the potential risks of veterinary medicinal products are adequately addressed in any application for marketing authorisation, and that the authorised conditions of use, including information on the product labelling, comply with legal requirements and the regulatory standards in place.

EU controls on the supply of veterinary medicines
Article 34 of new regulation specifies those medicines that are subject to veterinary prescription. This list includes medicines that:

- Contain narcotic drugs,
- Contain antimicrobials,
- Contain active substances that have been authorised for less than five years in the EU,
- Contain active substances that have a hormonal or thyrostatic action, or are beta-agonists,
- Are used for euthanasia.

The legislation also states that immunological veterinary medicines as well as veterinary medicines used in food-producing animals shall be classified as subject to veterinary prescription, unless Member

States choose to exempt certain VMPs from prescription control where all of the criteria listed in Article 34(3) of the regulation are fulfilled. These criteria include that the medicine:

- Does not present a direct or indirect risk, even if administered incorrectly, to the animal or animals treated, or to other animals, [or] to the person administering it, or to the environment,
- Does not contain any warnings of potential serious adverse events deriving from its correct use,
- Does not present a risk for public health as regards residues in food obtained from treated animals, even where the medicine is used incorrectly,
- Does not present a risk to public or animal health as regards the development of resistance, even where the medicine is used incorrectly.

The detailed operation of prescription within a Member State is subject to national control (e.g. who is entitled to dispense a veterinary prescription). Nationally, the legislative control framework is established by DAFM, with ethical obligations set by the Veterinary Council of Ireland and the Pharmaceutical Society of Ireland. The HPRA has no role in prescribing, dispensing, use and disposal of veterinary medicines.

HPRA Report on antiparasitic veterinary medicines intended for food-producing species

In 2019, the HPRA adopted a report on compliance of antiparasitic veterinary medicines with the criteria in the new regulation. The report sets out the background, evidence and findings clearly and plainly.

It is worth recalling that the standard EU legal requirement that all veterinary medicines used in food-producing animals are subject to veterinary prescription, and the criteria providing for exemption from prescription control, have been in place since 2006. However, since that time there have been a number of important developments:

- Regulation 2019/6 introduced new provisions for the authorisation of veterinary medicinal products that are targeted at limiting the development of antiparasitic resistance.
- Anthelmintic resistance has been widely reported in parasites of a number of livestock species in Ireland. The reports have been published in scientific, peer-reviewed journals. They highlight an increasing problem nationally.
- Globally, resistance to all currently used antiparasitic veterinary medicinal products has been demonstrated and reported on in scientific publications. Resistance is developing year-on-year and is now a significant animal health issue.
- All antiparasitic veterinary medicinal products for food-producing animals that have been authorised centrally by the EU Commission following the opinion of the European Medicines Agency, with the exception of medicines for bees, have been designated a prescription supply category.
- In recent years, different scientific and regulatory bodies, including the EMA, have flagged the problem and called for action to address it.

The report was compiled by an independent group of experts with expertise in the areas of parasitology, parasite resistance, environmental toxicology, regulatory affairs and animal health policy. The terms of reference and details are published in the report. In sum, the report sought to evaluate compliance of the medicines concerned against the legislative criteria to be fulfilled to permit exemption from prescription control. In conducting this work, the expert group reviewed and took account of relevant information in the scientific literature, both nationally and internationally. The report also considered the national regulatory framework under which the medicines are supplied currently in Ireland and in other EU Member States. The report also took into consideration the results of a stakeholder

consultation, undertaken by the HPRA in May/June 2019, in relation to the benefits and risks of any change to the current system, as well as stakeholders' views on an appropriate transition period, should a change be needed.

The report concluded that:

- There is widespread resistance to anthelmintics in parasites of livestock in Ireland,
- Anthelmintic resistance in parasites of other food-producing species has been demonstrated in European countries which have similar farming and animal husbandry conditions to those in Ireland,
- Resistance in ectoparasites to several veterinary drug classes has been identified in European countries that have similar farming and animal husbandry conditions to those in Ireland,
- Resistance to anticoccidial veterinary medicines has been shown in European countries that have similar farming and animal husbandry conditions to those in Ireland,
- Risks have been identified in regard to environmental safety of anthelmintic and ectoparasitic veterinary medicines, as well as for user safety, particularly if the medicines are administered incorrectly.
- In view of the widespread use of the medicines concerned over many years and the excellent record of compliance with the food residue standards, the availability of antiparasitic veterinary medicines through licensed merchant outlets does not present a particular risk to public health, as regards residues,
- The labelling of veterinary medicinal products is generally very comprehensive and includes information on warnings, contraindications, withdrawal periods and potential adverse reactions. The products concerned have been used for many years by farmers and end-users in compliance with the instructions. Noting that adverse reactions to veterinary medicinal products have been reported annually to the HPRA, the incidence of adverse reactions appears low and does not signal a particular problem associated with particular pharmaceutical forms, or a lack of skill or information in their use. Therefore, the availability of antiparasitic veterinary medicines through licensed merchant outlets does not present a particular risk in that respect,
- In general, the summary of product characteristics of antiparasitic veterinary medicines do not specify contraindications to the combined use of other veterinary medicinal products that are commonly used without prescription,
- Knowledge of parasitology and best practice in the use of antiparasitic veterinary medicines is not evenly distributed amongst stakeholders. This fact does not preclude that antiparasitic products should only be used correctly and when necessary.

The report concluded that having reviewed all the available evidence, antiparasitic veterinary medicines that are authorised without veterinary prescription for food-producing species do not comply with all the criteria set out in Article 34 of Regulation 2019/6. Consequently, the regulation requires that such VMPs are subject to prescription control. The report recommended that the maximum period until January 2022 be afforded to stakeholders so that veterinary practitioners, pharmacists, licensed merchants and farmers are able to engage with DAFM in relation to the elaboration and implementation of any new regulatory framework. The report also recommended that a multi-actor stakeholder approach be taken to elaborate national guidelines for sustainable parasite control, including the development of consistent scientifically-based advice on targeted selective treatments. The HPRA welcomes the opportunity provided by DAFM in establishing such a multi-actor approach, and is pleased to serve in this forum.

Conclusion

This is an exciting period in the history of veterinary medicines. The regulation offers new possibilities for innovation and for improving availability of veterinary medicines throughout the Union, while

safeguarding animal health, consumer health and environmental safety. For the first time, the veterinary medicines legislation has been customised to serve the needs of the sector. The new regulation recognises that the development of novel antibiotics and antiparasitic VMPs has proved to be elusive despite significant global R&D investment in recent decades.

We appreciate that addressing resistance is a challenging issue for many stakeholders and there is not a single easy solution to solve the issue. While incentivising the development of novel medicines, the regulation recognises that in the meantime we must do what is needed to preserve the effectiveness of current medicines into the future. The HPRA aims to play its part by ensuring that authorised medicines are safe and effective and that they comply with the regulatory standards in place and relevant national and European legislation.

We welcome the opportunity to provide additional information on this statement or to answer questions which the Chair or members of the committee may have.

Yours sincerely,

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