

**Report of the Task Force
on the method of supply of
antiparasitic veterinary medicinal
products that are intended for
food-producing species**

6 December 2019

Page 1 of 51

TABLE OF CONTENTS

EXECUTIVE SUMMARY

CHAPTER ONE: INTRODUCTION

- 1.1. Background
- 1.2. Preamble
- 1.3. Methodology and structure of this report

CHAPTER TWO: THE CURRENT SCIENTIFIC SITUATION

- 2.1 Introduction
- 2.2 The criteria set out in Article 34 of Regulation 2019/6
 - (a) Pharmaceutical forms requiring no particular knowledge or skill in using the products
 - (b) Products that do not present a direct or indirect risk, even if administered incorrectly
 - (c) Products that do not contain any warnings of potential serious adverse events deriving from its correct use
 - (d) Products that have been the subject of frequent adverse event reporting
 - (e) Products that refer to contra-indications to other products that are commonly used without prescription
 - (f) Risks for public health as regards residues
 - (g) Risks for public or animal health as regards the development of resistance
 - i. Anthelmintic resistance in food-producing animals
 - ii. Resistance to ectoparasitic drugs in food-producing animals
 - iii. Resistance to anti-coccidial veterinary medicines in food-producing animals

CHAPTER THREE: THE SUPPLY OF VETERINARY MEDICINAL PRODUCTS FOR FOOD-PRODUCING ANIMALS IN IRELAND AND OTHER EUROPEAN COUNTRIES

- 3.1 Current situation regarding the supply classification in Ireland
- 3.2 Position of products in other EU Member States
- 3.3 Developing trends in agriculture, veterinary medicinal products and animal diseases
- 3.4 Future developments affecting veterinary medicinal products as a result of Regulation 2019/6
- 3.5 Requirement of Regulation 2019/4

CHAPTER FOUR: STAKEHOLDER CONSULTATION, ANALYSIS OF BENEFITS AND RISKS OF MAINTAINING THE *STATUS QUO*, OPTIONS FOR CHANGE, AND LIKELY IMPACT

- 4.1 Introduction
- 4.2 Stakeholder consultation
- 4.3 Stakeholder views on maintaining the *status quo*
- 4.4 Stakeholder views on possible changes to the supply classification
- 4.5 Analysis and impact assessment by the Task Force
- 4.6 Perspectives of stakeholders on logistics of any change
- 4.7 Perspective of Task Force on logistics of any change

CHAPTER FIVE: CONCLUSIONS, RECOMMENDATIONS AND DATA GAPS

- 5.1 Conclusion
- 5.2 Recommendations
- 5.3 Data gaps

Appendix 1. Classification criteria in Article 34 of Regulation 2019/6

Appendix 2. Terms of reference

Appendix 3. Regulatory controls on the supply of veterinary medicines in Ireland

Appendix 4. Membership of the Task Force

GLOSSARY OF TERMS

ACVM	Advisory Committee for Veterinary Medicines of the HPRA
AMR	Antimicrobial resistance
BZ	Benzimidazole
CPD	Continuous professional development
CVMP	Committee for Medicinal Products for Veterinary Use (of the EMA)
DAFM	Department of Agriculture, Food and the Marine
EPA	Environmental Protection Agency
ERA	Environmental risk assessment
FEC	Faecal egg count
FECRT	Faecal egg count reduction test
FOCRT	Faecal oocyte count reduction test
HPRA	The Health Products Regulatory Authority
IMB	Irish Medicines Board (now the HPRA)
EMA	The European Medicines Agency
EU	European Union
LM	Licensed Merchant
LV	Levamisole
MAH	Marketing authorisation holder
MALDT	Micro-agar larval development test
ML	Macrocyclic lactone
MRL	Maximum residue limit
MS	Member State (of the EU)
NDAB	National Drugs Advisory Board (now the HPRA)
PBT	Persistent, bioaccumulative and toxic
POM	Prescription only medicine
POM(E)	Prescription only medicine exempt
PPE	Personal protective equipment
PS	Pharmacy sale
QQI	Quality and Qualifications Ireland
SPC	Summary of Product Characteristics
SQP	Suitably qualified person
TF	Task Force
TST	Targeted selective treatments
UK	United Kingdom
VPO	Veterinary Practitioner Use Only

EXECUTIVE SUMMARY

Most veterinary medicinal products that contain antiparasitic drugs are supplied in Ireland as non-prescription medicines. This has been the case for three or more decades, and dates back to a time when many classes of veterinary medicinal products used in Ireland could be freely supplied over the counter, without prescription.

In 2004 European legislation established a new requirement that all veterinary medicinal products that are intended for use in food-producing animals should be subject to veterinary prescription control; however, this requirement was nuanced by 2006 legislation which allowed for the maintenance of non-prescription status for certain veterinary medicinal products in European Member States which did not present a risk to human or animal health or to the environment, and which met the specified criteria for exemption from veterinary prescription (Appendix 1).

At that time the Department of Agriculture and Food advised that all existing veterinary medicinal products that were available without prescription met the criteria. The relevant European legislation has been subject to review and revision over recent years, culminating in the adoption of Regulation 2019/6 in January 2019. The Regulation comes into effect in January 2022 and is directly applicable throughout the European Union (EU). The criteria for exemption from prescription control set out in Regulation 2019/6 are very similar to those previously set out in Directive 2006/130/EC. However, since that time there have been a number of important developments:

- Anthelmintic resistance has been widely reported in parasites of a number of livestock species in Ireland. The reports highlight an increasing problem nationally.
- Globally, resistance to all currently used antiparasitic veterinary medicinal products has been demonstrated. Resistance is developing year-on-year and is now a significant animal health issue.
- Under existing EU legislation, veterinary medicinal products that contain new drugs that have not been authorised previously cannot benefit from the exemption from prescription supply for a 5-year period. This restriction has resulted in veterinary medicinal products that contain novel drugs being supplied only under prescription by veterinary practitioners, while existing veterinary medicinal products containing established drugs but that are also indicated for the same parasites, being supplied both through a wide variety of retail outlets (such as Licensed Merchants), as well as from veterinary practitioners.
- 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 a number of European Union focus meetings and publications on this topic have flagged the need for responsible use of antiparasitic veterinary medicinal products to safeguard the efficacy of the products concerned for the future and to halt the spread of resistance.
- Regulation 2019/6 introduced new provisions for the authorisation of veterinary medicinal products that are targeted at limiting the development of antiparasitic resistance.

At the request of the HPRA's Advisory Committee for Veterinary Medicines, a Task Force (TF) was established to review the available evidence and report on whether the products concerned remain compliant with the criteria contained in Article 34 of Regulation 2019/6 and to consider the likely impact of any change of the method of supply. The formulation of a national strategy to control resistance to antiparasitic medicines in parasites of food-producing animals, the provision of advice on prudent use of the products concerned, and the stimulation of improved reporting of suspected lack of efficacy or adverse reactions were not included in the terms of reference of the TF.

The TF reviewed a wide variety of information, including published literature, European Medicines Agency reports and HPRA databases. In addition, the TF engaged in a consultation with stakeholders

which demonstrated divided opinions on the benefits and risk of any change to the current supply regimen. Most stakeholders acknowledge the existence of anthelmintic resistance, but opinion is sharply divided on how best to address the issue. Indeed it is beyond the scope of this report to provide a blueprint for a system for the management of parasitic resistance in food-producing animals. That said, the report lays out a number of goals and policy options that can be considered for the management of the risks, and which are expected to provide the Department of Agriculture, Food and the Marine (DAFM) with principles upon which to build the complementary national legislation required to facilitate the implementation of Regulation 2019/6 in January 2022.

The TF concluded that the available evidence shows 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 anti-coccidial veterinary medicinal products 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 medicinal products, as well as for user safety, particularly if the products are administered incorrectly. However, evidence concerning environmental risks of anti-coccidial drugs is sparse,
- In view of the widespread use of the products concerned over many years and the excellent record of compliance with the food residue standards, the availability of antiparasitic veterinary medicinal products 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 national competent authority, 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 medicinal products 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.

In summary, the TF considers that the antiparasitic products that are supplied without a veterinary prescription do not comply with all of the criteria contained in Article 34 of Regulation 2019/6.

CHAPTER ONE: INTRODUCTION

1.1 Background

At their meeting on 13 February 2019, the HPRA's Advisory Committee for Veterinary Medicines (ACVM) established a Task Force (TF) to review the position of antiparasitic and anti-coccidial veterinary medicinal products for food-producing animals¹ against the criteria² in Regulation (EU) 2019/6 for exempting from the normal requirement of a veterinary prescription. The Authority of the HPRA endorsed the establishment of the TF at their meeting on 14 March 2019.

The criteria as set out in Regulation 2019/6 are very similar to those previously set out in Directive 2006/130/EC. Given the existence of widespread authenticated reports of anthelmintic resistance in livestock in Ireland in recent years as well as international concerns over the spread of resistance to ectoparasitic drugs, the ACVM considered it timely to review the position of the categorisation of antiparasitic products that are indicated for use in food-producing animals.

The Regulation 2019/6 comes into effect on 28 January 2022, and the period between now and then is expected to allow the necessary time for any adjustments in the national legislation and systems for control on distribution of the products concerned to be undertaken.

The Terms of Reference of the TF are attached as Appendix 2.

Note that the Terms of Reference do **not** request the TF to formulate a national strategy to control resistance to antiparasitic medicines in parasites of food-producing animals, or to promote better use of the products concerned, or to stimulate improved reporting of suspected lack of efficacy or adverse reactions, even though such objectives have significant merit. Rather the primary intent of this report is to address whether or not the products concerned fulfil the legal criteria for exemption from veterinary prescription.

1.2 Preamble

In accordance with national³ and European legislation⁴, any new veterinary medicinal product must be evaluated and granted a marketing authorisation before it can be placed on the market in Ireland. There are two main procedures under which the authorisations may be granted:

- a) The centralised procedure allows the marketing of a medicine on the basis of a single EU-wide assessment and marketing authorisation which is granted by the European Commission and is valid throughout the EU. Pharmaceutical companies submit a single authorisation application to the European Medicines Agency (EMA). Approximately 10% of all the marketing authorisations for veterinary medicinal products in Ireland relate to centrally-authorised products.
- b) A procedure where the national competent authority receives an application and grants a national marketing authorisation. This procedure may be coordinated where applications are submitted in other Member States using procedures known as the decentralised procedure or the mutual recognition procedure. The majority of products authorised in Ireland fall into this category. In Ireland, the Health Products Regulatory Authority (HPRA) is the competent authority for the assessment and authorisation of veterinary medicinal products.

¹ 'Food-producing animals means animals bred, raised, kept, slaughtered or harvested for the purposes of producing food, as defined by Article 2 of Regulation (EC) No. 470/2009.

² Criteria are set out in Appendix 1.

³ European Communities (Animal Remedies) (No. 2) Regulations 2007, S.I. No. 786/2007, as amended

⁴ Regulation (EC) No 726/2004 and Directive 2001/82/EC.

The market for veterinary medicinal products in Ireland is dominated by products used to control internal parasites⁵, being 27% of total sales in 2014, while the market for ectoparasitic drugs is reported to be less than 10% of the market.

Most antiparasitic veterinary medicinal products that are intended for use in food-producing animals have been available in Ireland without the requirement for a veterinary prescription for many decades. Since 2004, any new drug substance that is used for the first time in animals in the European Union (EU) is restricted to use under prescription, in accordance with the relevant EU legislation⁶. That same legislation requires that veterinary medicinal products for food-producing species should ordinarily be supplied under prescription, save where existing national provisions apply, or, where a Member State exempted the products concerned in accordance with the criteria set out in Directive 2006/130/EC⁷. The *raison d'être* of Directive 2006/130/EC is set out in recital clause (1), namely that '*certain substances contained in veterinary medicinal products for food-producing species do not present a risk to human or animal health or to the environment*', and hence could be exempt from the ordinary requirement that '*veterinary medicinal products may be dispensed to the public only against prescription*'.

On 11 October 2006, the Department of Agriculture and Food issued a press release⁸ that advised the legislative criteria set out in Directive 2006/130/EC would not require any existing off-prescription veterinary medicines in Ireland to be changed to requiring a prescription. The press release correctly noted that the appropriate classification of veterinary medicinal products was a matter for the national competent authority [now the HPRA], based on the risk/benefit profile of individual products. The national legislation that was adopted in 2007 provided that the method of supply of products concerned should be classified according to the risk to public health, animal health, animal welfare and the environment. Essentially those without risk were classified as 'Licensed Merchant' (LM), with other products for food-producing species being allocated supply routes of 'Pharmacy only sale' (PS), 'Prescription only medicine, exempt' (POM[E]), 'Prescription only medicine' (POM) or 'Veterinary practitioner use only' (VPO).

The methodology of conducting a benefit/risk assessment of a veterinary medicinal product has developed since 2007, with the publication of a 'recommendation document'⁹ by the EMA. For the purposes of this report, the definition of risk that is given in Directive 2001/82/EC is used; i.e. any risk relating to the quality, safety and efficacy of the veterinary medicinal product as regards animal or human health and any risk of undesirable effects on the environment. In addressing the issue of risk, the document advises that '*zero risk does not exist*'. Therefore, for the purposes of this report, the risk management measures set out in the Summary of Product Characteristics (SPC) and the product literature are assumed to operate effectively, save where data are available that shows this not to be the case.

The benefit/risk recommendation document also states '*the benefit-risk balance of a veterinary medicinal product may be re-evaluated at any time of the product's life cycle if occurrence of suspected adverse events makes it necessary. This should concentrate on the new information that has become available, including published post-marketing clinical studies that contain pharmacovigilance information or confirmation of efficacy, and in particular whether this information has an impact on the marketing authorisation*'.

⁵ Animal health market in Ireland, 2014, The Animal and Plant Health Association, <http://www.apha.ie/AboutUs/Markets.aspx>, accessed on 26/04/2019.

⁶ Article 67, Directive 2001/82/EC.

⁷ The criteria are set out in Article 2, Directive 2006/130/EC. They are similar to those set out in Regulation (EU) 2019/6, as set out in Appendix 1.

⁸ 194/06, Minister Coughlan welcomes EU decision on exemption criteria for veterinary medicines.

⁹ CVMP Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products, EMEA/CVMP/248499/2007, accessed on 23/04/2019.

Even if it was the case that few reports of anthelmintic resistance in parasites infecting food-producing species were reported in Ireland in 2006, in recent years evidence of such resistance has emerged (see chapter two). Moreover, there have also been reports in the published literature of growing levels of resistance in ectoparasites in the EU and globally. Furthermore, as one of the goals of Regulation 2019/6 is to address resistance to antiparasitic drugs it is timely for the HPRA to review the suitability of the current classification against the criteria set out in Regulation 2019/6, which have changed slightly over those given in Directive 2006/130/EC.

Regulation 2019/6 becomes directly applicable in Ireland on 28 January 2022, having already been adopted in January 2019. This will necessitate a review and revision of the current national legislation, including those provisions relating to the designation of the route of supply of veterinary medicinal products that are authorised nationally. In particular, it will no longer be possible for the competent authority [the HPRA] to specify the route of supply on the product label, as this will be outside the scope of the textual information that is permitted. It is expected that DAFM will consider this dilemma during the elaboration of the new complementary national legislation in the period to 2022.

1.3 Methodology and structure of this report

This report considers the available evidence for compliance of the products concerned with the criteria list in the regulation. This analysis has taken a number of sources of information:

- Published literature,
- EMA meeting reports and guidances,
- Databases on authorised veterinary medicinal products and on adverse reaction reports from the HPRA and EMA.

It also considers the national regulatory framework under which antiparasitic veterinary medicinal products are supplied currently in Ireland and in other EU Member States, as well as how that the framework is likely to change over the coming years. The report then considers the results of a stakeholder consultation, which was 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 also considers relevant experiences with other significant changes in regulatory requirements. The final chapter of the report comprises a conclusion, recommendations and data gaps.

CHAPTER TWO: THE CURRENT SCIENTIFIC SITUATION

2.1 Introduction

The objective of this chapter is to review and document the available evidence against the legal criteria for exempting veterinary medicinal products used in food-producing species from the requirement for a veterinary prescription, as set out by a derogation in Article 34(3) of Regulation 2019/6.

2.2 The criteria set out in Article 34 of Regulation 2019/6

Any veterinary medicine containing a new active substance must be assigned prescription control for at least a period of 5 years in accordance with the existing EU veterinary medicines legislation. This requirement is also carried through in Article 34(1)(f) of the Regulation, but a derogation is allowed when certain criteria are met, in accordance with Article 34(3). An application to down-regulate the product to a non-prescription status is possible after a 5 year period post-authorisation has elapsed. Such applications to the relevant competent authorities have been successful in relation to anti-coccidial veterinary medicinal products for food-producing animals in the past, as well as for antiparasitic medicines for companion animals.

Concerning the detailed conditions set out in the derogation (i.e. the criteria in Article 34(3)), the evidence for each is provided below, in the order set out in the article.

(a) Pharmaceutical forms requiring no particular knowledge or skill in using the products

All veterinary medicines carry some level of risk, but it is assumed for the sake of this exercise that farmers, professional animal keepers and horse owners have a certain level of knowledge and understanding in how the veterinary medicines that are purchased are to be used, and that they possess the necessary competence to administer the products properly. Moreover, for products that are authorised for non-prescription use the individual product labelling and product literature have been considered and approved by the competent authority as being understandable to non-veterinary practitioner users. Occasional concerns on the safety of use of anthelmintic boluses have been raised with the HPRA or its predecessors the Irish Medicines Board (IMB) and the National Drugs Advisory Board (NDAB) several years ago, but there are no recent reports of adverse reactions.

Conclusion on pharmaceutical forms used

Acknowledging that in the strict sense the use of all veterinary medicinal products requires a certain level of knowledge and skill, the available evidence does not indicate a problem with regard to the use of the **pharmaceutical forms** concerned. Therefore, the products concerned can be considered to comply with this criterion.

(b) Products that do not present a direct or indirect risk, even if administered incorrectly

All veterinary medicines carry some level of risk. However, it is assumed in the context of this report that users have a certain level of understanding in how the products are to be used and will follow the instructions for use given either orally at the point of sale or as written on the product labelling and literature.

Expected risks that might occur under field use are routinely considered as part of the assessment by the competent authority prior to approval of the marketing authorisation. Arising from the risk assessment, mitigation measures are established and stated clearly in the product literature (e.g. use of gloves when administering products that might pose risks for human health, environmental warnings for disposal of spent sheep dip, etc.).

Risks, in this case, fall into four categories:

- i. Risk to the target animal. In general terms, the classes of veterinary medicine concerned do not have a low therapeutic index (margin between recommended dose and dose at which side

- effects are seen), or carry a risk to particular sub-groups of animals (very young or pregnant animals),
- ii. Risk to the user. This risk may be specific to the active substance or be related to the individual formulation or pharmaceutical form. Some active substances are more toxic than others, however, the extent of user exposure will be influenced by the concentration present, as well as the means by which it is packaged and made available to animals. Concentrated formulations containing active substances that are authorised for dilution for incorporation into sheep dips, as well as premixes and pour-on formulations represent particular risks for users. Some of these risks are mitigated by the use of personal protective equipment (PPE) and/or other risk management measures that are specified on the product labelling and SPC.
 - iii. Risk to the consumer. Consumer safety for all veterinary medicines is assured through a combination of record keeping and monitoring of foodstuffs for residues. Even in respect of veterinary medicinal products that have been restricted to supply under prescription the animal owner/farmer is ultimately responsible for ensuring compliance with the withdrawal period(s). Farmers are keenly aware of their responsibilities in this area. The available evidence from the annual national official testing of foods or food produce shows an extremely high level of compliance regarding residues of veterinary medicinal products¹⁰.
 - iv. Risk to the environment. The fate of active substances that are used in veterinary medicinal products is evaluated by the HPRA during the assessment of the product. Where a hazard is identified, an exposure assessment is made and appropriate risk mitigation measures are described in the product SPC and labelling. An unacceptable risk for the environment is not expected where veterinary medicines are used properly, in accordance with the SPC.

From a review of 100 products¹¹ out of a total of approximately 290 products containing antiparasitic substances that have been authorised nationally by the HPRA, it is clear that all veterinary medicinal products carry comprehensive warnings, including:

- contraindications,
- special species warnings,
- special precautions for the product user,
- warnings on interactions,
- warnings on use during pregnancy, lay or lactation,
- warnings relating to over-dosage,
- information on environmental disposal, and
- information on withdrawal periods that must be followed.

However, the number and detail of the warnings do not necessarily correlate with the toxicity and risk of individual drug substances (or drug combinations) or with the pharmaceutical forms being used. Rather, they appear to reflect the fact that the products concerned were approved nationally over different years or decades (some being the product of joint assessments carried out in several EU Member States), and that different regulatory approaches were taken to the labelling of individual products compared to others.

It is considered that national pharmacovigilance experience represents a more robust means to determine the evidence of direct and indirect risks than a review of the product SPCs, as it reflects reports made under actual use conditions. The risk to animals and consumers will be considered under separate subheadings later in this chapter.

Concerning risks to humans, a review of the HPRA's database of human reactions to antiparasitic veterinary medicinal products used for food-producing species for the period 1 January 2014 to 4 June

¹⁰ National residue control plan report 2018.

<https://www.agriculture.gov.ie/media/migration/animalhealthwelfare/veterinary/residues/2018Report310719.pdf>
Accessed 15/08/2019

¹¹ Products chosen to reflect each active substance, drug combination, pharmaceutical form, and species.

2019 reveals that there have been five reports submitted. The reported symptoms include injection site pain, malaise, nausea, disorientation, dry mouth, salivation, dermatitis, itchiness and reddening of the skin. All human reactions are classified as serious, even if it is not clear whether in these cases human exposure would have been avoided should the products have been restricted to prescription control (the products concerned would still have been administered by users).

A review of the available literature has shown few reports of adverse effects in humans to the use of veterinary antiparasitic drugs. Neuropsychological effects of long-term exposure in humans to organophosphates in sheep dips¹² have been documented, however. It should also be noted that the HPRA has, following a review of the scientific literature regarding short-term and long-term adverse events in humans using sheep dips, issued a safety advisory notice regarding the risk of human adverse reactions¹³. Additionally, Hellen and Ni Raghallaigh¹⁴ advised that misuse of horse wormers as a cheaper alternative to prescribed human medicines in dermatology patients might lead to the development of ivermectin resistance in humans.

The available evidence, therefore, points to a degree of risk for product users.

Deliberate misuse (birds of prey)

Based on data provided by DAFM in relation to the investigation of deaths of birds of prey in Ireland in the period 2011 to 2018, nitroxylnil has been implicated in six percent (14 cases) of the incidents investigated. By contrast, rodenticides have been identified as the causal agent in 60% of all incidents during that period. For completeness of information, it is understood that new controls in the supply of rodenticides, including specific record keeping and training requirements for sellers, has been introduced by DAFM since 1 January 2018.

Environmental risk

The environmental fate of pharmaceuticals has been the subject of interest by the EU Commission¹⁵, particularly over recent years¹⁶. Antiparasitic medicines have been identified as posing environmental risks under specific exposure scenarios¹⁷. Since 1992, every veterinary medicinal product that is authorised must contain an environmental risk assessment (ERA), prior to being approved by the competent authority. The legislation¹⁸ requires that the assessment be conducted in two phases:

- In phase I, the potential extent of exposure of the product, its active substances and relevant metabolites is investigated. This phase takes into consideration the physical/chemical, and other properties of the drug, as well as the dosage, duration, method and frequency of therapy, and weight and nature of the target animals,
- In phase II, investigation or consideration of exposure in soil, water and air, as well as effects on aquatic and other non-target organisms is assessed.

¹² Neuropsychological effects of long-term exposure to organophosphates in sheep dip. 1995. Stephens, R., Spurgeon, A., Calvert, I.A., Beach, J., Levy, L.S., Berry, H. and Harrington, J. M., Lancet, 345; 1135.

¹³ Care in use and disposal of sheep dips. <http://www.hpra.ie/homepage/veterinary/special-topics/care-in-use-and-disposal-of-sheep-dips>

¹⁴ Hellen, R. and Ni Raghallaigh, S., 2019, Misuse of veterinary wormers in self-medication of rosacea and scabies. British Journal of Dermatology, 180 (4); 955.

¹⁵ EU Commission Strategies against chemical pollution of surface waters, <http://ec.europa.eu/environment/water/water-dangersub/index.htm#strategic>. Accessed 04/07/2019.

¹⁶ EU Commission Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee. 11.3.2019. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52019DC0128&from=EN>. Accessed 04/07/2019.

¹⁷ EU Commission Final report; Options for a strategic approach to pharmaceuticals in the environment. July 2018. <https://publications.europa.eu/en/publication-detail/-/publication/5371e7bd-25db-11e9-8d04-01aa75ed71a1/language-en> Accessed 04/07/2019.

¹⁸ Commission Directive 92/18/EEC.

The Commission acknowledges that some pharmaceuticals that were put on the market years ago were not subject to an adequate ERA as part of the authorisation process, and that monitoring of pharmaceuticals in the environment is 'very limited'¹⁵.

EMA guidelines set out the data requirements for the ERA¹⁹. While the guidelines apply to all veterinary medicinal products, they acknowledge that antiparasitic veterinary medicinal products pose specific ecotoxicity concerns, especially when used in animals at pasture, because many of these products are pharmacologically active against organisms that are biologically related to pasture invertebrates.

Of particular note is the EU Commission decision on moxidectin²⁰, which followed the opinion of the EMA that, based on the available data, moxidectin fulfils the criteria for persistence, bioaccumulation and toxicity according to the results of the laboratory studies and consequently, had to be classified as a persistent, bioaccumulative and toxic (PBT) substance. Further, it noted that '*a risk for dung fauna [had] been identified*'²¹. In an earlier paper²², the EMA advised that '*a preliminary screening of active substances used in veterinary medicinal products identified up to 20 candidate substances which are potentially PBT*' but added that data to conclude on the PBT status of these substances were not available. It also stated that '*almost all potential PBT substances identified to date [were] parasiticides, the majority of which [were] authorised for use in food-producing species*'. The EMA document also drew attention to those parasiticides used to control sea lice in Atlantic salmon as having undesirable (non-target) effects when released into the aquatic environment.

The quantity of drug entering the environment depends on a number of factors. Boxall *et al.*²³ reported that the impact of veterinary medicines on the environment will depend on physicochemical properties, amount used and method of administration, treatment type and dose, animal husbandry practices, manure storage and handling practices, metabolism within the animal, and degradation rates in manure and slurry. The authors also report that once released to the environment, other factors such as soil type, climate, and toxicity also determine the environmental impact of the compound. The importance of individual routes into the environment for different types of veterinary medicines varies according to the type of treatment and livestock category. Treatments used in aquaculture have a high potential to reach the aquatic environment. The main routes of entry to the terrestrial environment are from the use of veterinary medicines in intensively reared livestock, *via* the application of slurry and manure to land, and by the use of veterinary medicines in pasture-reared animals where pharmaceutical residues are excreted directly into the environment. Veterinary medicines applied to land *via* spreading of slurry may also enter the aquatic environment indirectly *via* surface runoff or leaching to groundwater. Topical treatments are expected to have greater potential to be released to the environment than treatments administered orally or by injection because the dosage of drugs in pour-on formulations needed to treat or prevent infections is generally higher than that needed for injectable or oral formulations with the same drug. The authors report that monitoring studies demonstrate that sheep dip chemicals,

¹⁹ EMA Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL 38. 26 June 2016. <https://www.ema.europa.eu/en/environmental-impact-assessment-veterinary-medicinal-products-support-vich-guidelines-gl6-gl38>. Accessed 02/07/2019.

²⁰ European Commission decision (2017)6577 of 25 Sep 2017 on moxidectin. <https://ec.europa.eu/health/documents/community-register/html/vo26301.htm>. Accessed 04/07/2019.

²¹ EMA. 2017, Scientific conclusions and grounds for amendment of the summaries of product characteristics, labelling and package leaflets for moxidectin. https://www.ema.europa.eu/en/documents/referral/moxidectin-article-35-referral-annex-i-ii-iii-iv_en.pdf. Accessed 04/07/2019.

²² EMA Reflection paper on the authorisation of veterinary medicinal products containing (potential) persistent, bioaccumulative and toxic (PBT) or very persistent, bioaccumulative and toxic (vPvB) substances. 18 February 2016. EMA/CVMP/448211/2015. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-authorisation-veterinary-medicinal-products-containing-potential-persistent_en.pdf Accessed 4/7/2019.

²³ Boxall, A.B.A, Fogg, L.A., Blackwell, P.A, Kay, P, Pemberton, E.J., and Croxford, A. 2004. Veterinary medicines in the environment. *Reviews of Environmental Contamination and Toxicology*. 180; 1.

antibiotics, sea lice treatments, and anthelmintics have been found in soils, groundwater, surface waters, sediment, or biota. However, they advise that the degree to which veterinary medicines adsorb to particulates varies widely between compounds and according to the soil type. The authors report that transport of particle-associated drug substances from soil to surface waters has also been demonstrated. Veterinary medicines can persist in soils for days to years, and half-lives are influenced by a range of factors including temperature, pH, and the presence of manure. The persistence of major groups of veterinary medicines in soil, manure, slurry, and water varies across and within classes. Ecotoxicity data are available for a wide range of veterinary medicines. The acute and chronic effects of avermectins and sheep dip chemicals on aquatic organisms are well documented, and these substances are known to be toxic to many organisms at low concentrations (ng L^{-1} to $\mu\text{g L}^{-1}$). Concerns have also been raised about the possibility of indirect effects of these substances on predatory species (e.g., birds and bats).

Kools *et al.*²⁴ estimated that antiparasitic products account for the second-highest use of veterinary medicines in the European Union (being about 3.5% of the estimated use of antibiotics). However, the authors cautioned that this estimate is based on 2004 data that are extrapolated based on foodstuff production in the EU. In a report to the UK government dating from 2002, Boxall *et al.*²⁵ identified a number of drugs for high priority evaluation based on application of the EMA's phase I assessment. The drugs identified included diazinon and cypermethrin, where UK water quality surveys date from the 1980s and 1990s showed a number of serious pollution incidents involving diazinon, propetamphos, fenchlorphos, chlorfenvinphos and synthetic pyrethroids. Additional antiparasitic products that were identified as potentially high priority, but requiring further data included (ranked on the basis of annual usage in the UK): morantel, flumethrin, triclabendazole, fenbendazole, levamisole, ivermectin, nitroxylin, toltrazuril, diclazuril, phosmet, piperonyl butoxide, amitraz, deltamethrin, cyromazine, and emamectin benzoate.

Horvat *et al.*²⁶ reported that anthelmintics are expected to have possible impacts on both the terrestrial and aquatic environments. Following treatment of animals with these compounds, residues could occur in the environment by excretion, either unchanged or as metabolites, which might retain antiparasitic activity. The amount entering the environment depended on husbandry system and the stocking densities.

Jacobs and Scholtz²⁷ in a review article reported that residues of avermectins (ivermectin, eprinomectin and doramectin) and milbemycins (moxidectin) in cattle dung had a negative effect on the entire assemblage of insects that inhabit and feed on dung, which over time would result in decreased dung beetle populations and the rate of dung degradation.

Gilbert *et al.*²⁸ found that the density of arthropod larvae in artificial pooled dung pats obtained from cattle on the island of Islay was significantly reduced when the animals had been treated in the previous 4-5 days with triclabendazole or deltamethrin, and by as much as 86% when they were treated with

²⁴ Kools, S.A., Moltmann, J.F. and Knacker, T., 2008, Estimating the use of veterinary medicines in the European Union, *Regulatory Toxicology and Pharmacology*, 50(1); 59.

²⁵ Boxall, A.B.A., Fogg, L., Blackwell, P.A., Kay, P., Pemberton, E.J., 2002, *Review of Veterinary Medicines in the Environment*. Environmental Agency, Swindon, UK.

²⁶ Horvat, A.J.M., Petrovic, M., Babic, S., Pavlovic, D.M., Asperger, D., Pelko, S., Mance, A.D. and Kastelan-Macan, M., 2012, Analysis, occurrence and fate of anthelmintics and their transformation products in the environment. *Trends in Analytical Chemistry*, 31; 61.

²⁷ Jacobs, C. T. and Scholtz, C.H., 2015, A review on the effect of macrocyclic lactones on dung-dwelling insects: Toxicity of macrocyclic lactones to dung beetles. *Onderstepoort Journal of Veterinary Research*, 82(1); 858.

²⁸ Gilbert, G., MacGillivray, F.S., Robertson, H.L. and Jonsson, N.N., 2019. Adverse effects of routine bovine health treatments containing triclabendazole and synthetic pyrethroids on the abundance of dipteran larvae in bovine faeces. *Scientific Reports*, 13(9); 4315.

both drugs, when compared to unmedicated controls. The authors opined that the differences in density of larval arthropods in faeces from animals exposed to the treatments in the study were most likely a consequence of impaired development and survival in faeces from treated animals rather than reduced attractiveness to ovipositioning adults of faeces from cattle exposed to the treatments. The authors concluded that the reduction in arthropods by the triclabendazole and deltamethrin treatments is suggestive of a correlation with the decline in the population of endangered red-billed croucher (*Pyrrhocorax pyrrhocorax*), which are dependent on dung invertebrates as a feed source.

Powell *et al.*²⁹ reported that synthetic pyrethroids (e.g. deltamethrin and permethrin) have a long half-life in the environment (cited as being typically 33 days), and are lethal to fish at a concentration of two parts per trillion, equating with one part deltamethrin per 5×10^{11} parts water). They also reported that synthetic pyrethroids have been responsible for the widespread death of invertebrates and other wildlife in three rivers in Wales (it should be noted that cypermethrin has also been used in forestry management for pest control³⁰ and this type of usage has been shown to contribute to pollution of rivers). The authors also report on the known toxicity of avermectins to dung-degrading insects, their potential toxic effects to birds and their adverse effects on aquatic ecosystems over the long term (cited as being greater than 229 days).

Beynon³¹ reported that, with the exception of the impact of spent sheep dip on aquatic systems, the literature on the environmental impacts of sheep ectoparasiticides is sparse. From her review of the literature, she concluded that '*synthetic pyrethroids and organophosphates pose risks to dung, soil and aquatic fauna*'. The UK's national competent authority for veterinary medicines, the Veterinary Medicines Directorate suspended the marketing authorisations for cypermethrin sheep dips in 2006 following evidence that the use of cypermethrin sheep dips was causing environmental pollution in watercourses³².

In Ireland, the Environmental Protection Agency (EPA) monitors a number of pesticide-related substances in groundwater, including cypermethrin. The EPA reported no detection of cypermethrin in its most recent data collected in 2014³³, although some exceedances of EU Environmental Quality Standards for cypermethrin in surface water sources had been reported, in Co. Donegal, albeit at very low levels. It is also known that, as part of the water framework directive, monitoring of transitional and coastal waters has been undertaken nationally since 2016, but it has been stated that the test methods for cypermethrin are not currently capable of detecting minute levels that can adversely affect the environment, including aquatic invertebrates and fish. Furthermore, it is reported³⁴ that there is no comprehensive monitoring of sheep dip disposal, notwithstanding that '*sheep dip is a hazardous waste and should not be landspread in the absence of a waste licence*'.

Conclusion on direct or indirect risk

From the non-exhaustive scientific evidence, it is clear that the antiparasitic veterinary medicines that are intended for food-producing species cannot be considered to comply with this criterion in the strict

²⁹ Powell, K., Foster, C. and Evans, S., 2018, Environmental dangers of veterinary antiparasitic agents, *Veterinary Record* 183; 599

³⁰ Environmental Agency Wales. 2010, Cypermethrin use in forestry and its impact on Welsh streams. <http://aquaticcommons.org/10900/1/01->

[An evaluation of the impact of cypermethrin use in forestry on Welsh streams.pdf](#). Accessed 09/07/2019.

³¹ Beynon, S.A., 2012, Potential environmental consequences of administration of ectoparasiticides to sheep, *Veterinary Parasitology* 189; 125.

³² VMD suspends marketing authorisations for cypermethrin sheep dips, 2006, *Veterinary Record*, 166(9); 282

³³ Regan, F., Jones, L., Ronan, J., Crowley, D., McGovern, E. and McHugh, B. 2012, Role of passive sampling in screening and monitoring of new and emerging chemicals. EPA Research, Report No. 243. http://www.epa.ie/pubs/reports/research/water/Research_Report_243.pdf. Accessed 15/08/2019.

³⁴ EPA, 2008, National Hazardous Waste Management Plan 2008-2012. A Report by the Environmental Protection Agency, Wexford. <https://www.epa.ie/pubs/reports/waste/haz/NHWMP2008.pdf>. Accessed 09/07/2019.

sense, as risks have been identified with the use of anthelmintic and ectoparasitic products, especially regarding the environment, but also for user safety and, rarely, for the purpose of deliberate poisoning of wildlife. Specific data concerning environmental risks of anti-coccidial drugs are sparse, but it is known from the SPC of a product containing toltrazuril that a metabolite of the drug is very persistent in soil and has adverse effects on plants.

(c) Products that do not contain any warnings of potential serious adverse events deriving from its correct use

A review of a selection of the SPCs of the authorised products concerned shows that a significant number of products contain warnings of potentially serious adverse events e.g. *levamisole can cause idiosyncratic reactions and serious blood disorders in a very small number of people....*' (Vermisole worm drench), *'phoxim is an organophosphorus compound. Do not use if under medical advice not to work with such compounds.....'* (ByeMite), *'slightly irritant to the skin and mucous membranes'* (Bayticol 10 mg/ml Pour-on),

As pointed out in the previous section, the warnings of individual products are not well correlated to the potential toxicity and risk of exposure to the veterinary medicinal products, and similar products contain different degrees of information. To rigidly apply this criteria would result in some products being classed as requiring prescription, while other similar products containing the same active substances and in the same strengths and presentations would not. From a review of suspected adverse reactions that have been submitted to the HPRA over the last 5 years, there is not any robust evidence to indicate that the products with more comprehensive warnings are associated with lower adverse reactions being reported.

Conclusion on warnings of potentially serious adverse events

Acknowledging that many veterinary medicinal products carry warnings of potentially serious adverse events even when used correctly, the available evidence does not indicate a particular problem with safety in the use of the products concerned. Therefore, the products concerned can be considered to comply with this criterion.

(d) Products that have been the subject of frequent adverse event reporting

An adverse event is defined in Regulation 2019/6 as:

- a) any unfavourable and unintended reaction to a veterinary medicinal product;
- b) any observation of a lack of efficacy following its administration to an animal, whether or not in accordance with the summary of product characteristics;
- c) any environmental incidents observed following administration to an animal;
- d) any noxious reaction in humans exposed to a veterinary medicinal product;
- e) any finding of a pharmacologically active substance or marker residue in a product of animal origin exceeding the maximum levels of residues established in accordance with Regulation (EC) No 470/2009 after the set withdrawal period has been respected;
- f) any suspected transmission of an infectious agent via a veterinary medicinal product;
- g) any unfavourable and unintended reaction in an animal to a medicinal product for human use.

A review of the EMA's pharmacovigilance bulletins³⁵, which detail veterinary pharmacovigilance activities in respect of centralised antiparasitic veterinary medicines that are authorised throughout the EU, as well as pharmacovigilance issues concerning nationally authorised products in the EU Member States in the period since 2014 has shown that;

- In 2018, suspected reports of lack of efficacy due to resistance to monepantel were reported.

³⁵ Public bulletins summarises information in relation to monitoring activities of the EMA.

<https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation/pharmacovigilance/public-bulletins-veterinary-pharmacovigilance> Accessed on 28/5/2019.

- In 2017, suspected reports of death, lethargy, anorexia, egg drop, enteritis, hepatobiliary disorders and splenomegaly were reported concerning fenbendazole in poultry. Suspected reports of lack of efficacy to monepantel were also reported.
- In 2016, in light of suspected reports of resistance to monepantel, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that amendments to the wording of the product literature was necessary to highlight the fact that *'isolated cases of resistance against monepantel have been identified within the European Union'*.
- In 2015 suspected reports of lack of efficacy to monepantel were reported. It was also reported that, as a consequence of pharmacovigilance data in France relating to the use of an ivermectin/closantel pour-on solution in cattle, *'adverse events including neurological signs and gastrointestinal disorder some of which had a fatal outcome'* had been reported. That signal led the CVMP to improve the product information for the products involved.
- In 2014, no explicit mention of suspected reports involving antiparasitic drugs intended for use in food-producing species was made.

In addition, a review of the HPRA's database of adverse reactions reported from Ireland has been conducted, using the EU causality assessment approach³⁶. This methodology takes into account the duration of time between the treatment and the reaction seen, the known pharmacology and toxicology of the drug, the clinical signs found, the previous knowledge of similar reports, exclusion of other causes, completeness and reliability of the data in the reports etc. From the review of the reports were classed either as 'possibly' or 'probably' linked to treatment³⁷ with antiparasitic veterinary medicinal products for food producing species for the period 2014 – 2018 inclusive the following information was identified:

- There have been 69 reports of suspected adverse reactions in cattle, involving some 392 reactions and 54 deaths,
- There have been 13 reports of suspected adverse reactions in sheep, involving some 182 reactions and 32 deaths,
- There have been 9 reports of suspected adverse reactions in bees, some of which involved bee or colony deaths,
- There has been 1 report of suspected adverse reaction in horses, involving a single animal, which survived.

In addition, the review of the HPRA database has identified the following information in respect of reports of suspected lack of efficacy to antiparasitic veterinary medicinal products for food producing species which have been classified as possibly relating to treatment:

- During 2018, there were 9 reports, involving the use of cypermethrin, halofuginone, imidocarb, ivermectin, moxidectin, oxfendazole, and closantel in cattle and sheep,
- During 2017, there were 5 reports, involving the use of cypermethrin, ivermectin, levamisole, closantel and triclabendazole in cattle and sheep,
- During 2016, there were 4 reports, involving the use of diazinon, cypermethrin, dicyclanil, ivermectin, and albendazole in cattle and sheep,
- During 2015, there were 6 reports, involving the use of deltamethrin, cypermethrin, halofuginone, ivermectin and clorsulon in cattle and sheep,

³⁶ EMA recommendation on harmonising the approach to causality assessment of adverse events to veterinary medicinal products. EMA/CVMP/PhVWP/552/2003 – Rev.1

https://www.ema.europa.eu/en/documents/scientific-guideline/recommendation-harmonising-approach-causality-assessment-adverse-events-veterinary-medicinal_en-0.pdf Accessed 27/06/2019.

³⁷ Causality of 'probable' is allocated where all of the following conditions apply there is an associative connection in time, the adverse event fits the pharmacological/toxicology profile of the product, there is no other equally plausible explanation and there is no indication that the information provided is insufficient or unreliable. Causality of 'possible' is allocated where associative connection in time or associative connection to the pharmacological/toxicology profile of the product is weaker, but where there is no other equally plausible explanation and there is no indication that the information provided is insufficient or unreliable.

- During 2014, there were 7 reports, involving the use of halofuginone, ivermectin, albendazole, levamisole, closantel, clorsulon and nitroxylnil in cattle.

While reports of lack of efficacy may signal resistance, there are many other possible causes (e.g. under-dosing, use of products beyond their expiry date etc.). It should also be noted that the pharmacovigilance system is not an efficient method to accurately monitor antiparasitic resistance in the field, as many events go unreported to veterinary practitioners, other health care professionals and the HPRA.

A complicating factor in assessing the merits of selectively assigning causality to a particular class of antiparasitic product, for the purposes of this particular criterion is to define what constitutes 'frequent' reporting. It would be logically expected that even when the incidence of adverse event reports between antiparasitic classes is identical, the greater the use of a particular veterinary medicinal products the greater will be the number of reports associated with that product, compared to a product that is seldom used.

Conclusion on products that have been subject to frequent adverse event reporting

Acknowledging that there have been a number of reports of adverse events concerning antiparasitic veterinary medicines in Ireland and the EU over recent years, given that the products concerned are very widely used, the available evidence does not indicate a particular problem. Therefore, the products concerned can be considered to comply with this criterion.

(e) Products that refer to contra-indications to other products that are commonly used without prescription

A review of a cross-sectional sample of 100 antiparasitic products from the HPRA's database of authorised veterinary medicinal products (representing approximately 22% of all such products) shows that none has a specific contraindication to other commonly used [veterinary medicinal] products.

Most antiparasitic products carry contraindications regarding use in animals with known hypersensitivity to the active substances, while some carry a contraindication for use in non-target species (e.g. Endex 8.75%, VPA 22020/36/1 has a contraindication for use in goats, many products containing ivermectin are contraindicated in dogs) or use in various categories of animals (e.g. Embotape Oral Paste, VPA 220133/15/1, has a contraindication on use in severely debilitated animals as well as a warning that '*combined use of pyrantel and levamisole or piperazine is not recommended*'). Other veterinary medicinal products contain advice regarding possible interactions e.g. for some products containing levamisole (e.g. Levacide Injection 75 mg/ml, VPA 22664/25/1) there is a statement that '*concurrent treatment with products containing organophosphorus compounds or diethylcarbamazine citrate should be avoided. These compounds should not be administered within a period of 14 days before or after treatment with levamisole*'. Interestingly, this statement is not present in all products containing levamisole, however. While there are a number of authorised veterinary medicinal products that contain organophosphates, none contains diethylcarbamazine citrate. Other products also contain contraindications relating to use of products that should only be available following prescription e.g. Cydectin 1% for Sheep, VPA 10387/14/1 carries a contraindication on use in animals with a history of previous vaccination against footrot, as '*such use may result in anaphylactic-type reactions, including dyspnoea, ataxia, depression, death and abortions*'. Footrot vaccines are subject to prescription, although the products may be dispensed from licensed merchant outlets.

Given the inconsistency in the number and type of contra-indications between products that contain the same antiparasitic drug in the same dosage forms (e.g. oral drenches) and that are indicated for the same target species, it is concluded that the allocation of contra-indications and warnings to products has not been based solely on the toxicity of the drug and the associated risks, but to some other extraneous reasons. These reasons might be associated with the timing of the date of the original

marketing authorisation (newer products tend to have more warnings compared to those authorised decades ago), whether the marketing authorisation relates to a product authorised only in Ireland or to one that has been harmonised with several other Member States, or whether it is due to a precautionary approach to communicating risks by the marketing authorisation holder.

Conclusion on products that refer to contraindications to other products that are commonly used without prescription

Acknowledging that the product literature of many veterinary medicinal products bear information on contraindications, very few cite absolute contraindications to other authorised veterinary medicines that are commonly used without prescription. The available evidence does not indicate a particular problem with regard to the safe use of the products concerned. Therefore, the products concerned can be considered to comply with this criterion.

(f) Risks for public health as regards residues

The risk for consumer health as regards residues is linked to the toxicity of the drug residue(s) in the product and the likelihood of consumer exposure to that residue in animal meat, milk, eggs or other tissues. In respect of all veterinary medicinal products that are used in food-producing animals, the legislation³⁸ requires that the residues of veterinary medicinal products remaining post-treatment in foodstuffs of animal origin are scientifically assessed. Only those substances that have received a positive opinion by the EMA are permitted to be used in veterinary medicinal products. Maximum residue limits (MRLs) are established for those substances where residues of the veterinary medicine are of concern. The MRLs are used by the competent authorities to set the withdrawal periods for the products in question. The withdrawal periods are established by national competent authorities (i.e. the HPRA in the case of products authorised in Ireland) based on EU standards and norms, using conservative methodologies that are designed to protect public health. MRLs are also used by the competent authorities of the State to monitor the safety of the food supply, in accordance with the national residue control plan³⁹.

A recent national residue plan report concerning Ireland⁴⁰ states that the '*overall rate of compliance remains at an extremely high level of 99.7%*' and that, of the 51 samples found that were non-compliant, '*risk evaluations by the Food Safety Authority of Ireland were carried out in response to each result and it was found that there was no unacceptable food safety risk to consumers*'. However, it is noted:

- In the 2018 report it is stated that in the bovine, ovine and milk sectors, 7 samples (out of a total of 7224) contained residues of anthelmintics which '*indicated that specified post-treatment withdrawal periods had not been observed or incorrect administration had occurred*'.
- In the 2017 report it is stated that in the bovine, ovine and milk sectors, 18 samples (out of a total of 7708) contained residues of anthelmintics which '*indicated that specified post-treatment withdrawal periods had not been observed*'.
- In the 2016 report it is stated that in the bovine, ovine, porcine, equine and milk sectors, 17 samples (out of a total of 8118) contained residues of which '*indicated that specified post-treatment withdrawal periods had not been observed*'.
- In the 2015 report it is stated that in the bovine, ovine, equine and milk sectors, 7 samples (out of a total of 8799) contained residues of anthelmintics which '*indicated that specified post-treatment withdrawal periods had not been observed*'.

³⁸ Regulation (EU) No 37/2010 regarding the classification of the pharmacologically active substances in foodstuffs of animal origin

³⁹ The national residue control plan is drawn up annually between government and the EU Commission. See <https://www.agriculture.gov.ie/animalhealthwelfare/veterinarymedicinesresidues/residues/>

⁴⁰ 2017 National Residue Control Plan Report 2017.

<https://www.agriculture.gov.ie/media/migration/animalhealthwelfare/veterinary/residues/2017Report120718.pdf>
Accessed 28/05/2019

- In the 2014 report it is stated that in the bovine, ovine, equine and milk sectors, 10 samples (out of a total of 8062) contained residues of anthelmintics which '*indicated that specified post-treatment withdrawal periods had not been observed*'.
- In the 2013 report it is stated that in the ovine and milk sectors, 4 samples (out of a total of 8791) contained residues of anthelmintics, which '*indicated that specified post-treatment withdrawal periods had not been observed*'.
- In the 2012 report, it is stated that 6 samples of ovine or equine tissues (out of a total of 9,442) contained residues of anthelmintics, which '*indicated that specified post-treatment withdrawal periods had not been observed*'.
- In the 2011 report, it is stated that 7 samples (out of 9,341) contained residues of anthelmintics, which '*indicated that specified post-treatment withdrawal periods had not been observed*'.
- In the 2010 report, it is stated that four sheep tissue samples (out of 12,500 samples) contained residues of anthelmintics, which '*indicated that specified post-treatment withdrawal periods had not been observed*'.

Conclusion on risks for public health as regards residues

Even if no specific residue violations concerning ectoparasitic and anti-coccidial drugs in Ireland have been detected, and even if ultimately compliance with the stated withdrawal period for any veterinary medicinal product is the responsibility of the user/farmer, irrespective of whether the veterinary medicine is supplied through licensed merchant outlets directly or under veterinary prescription, the available evidence indicates that a few cases of residues of anthelmintics have been found during routine testing every year. However, overall it is concluded that there is an excellent record of compliance with the food residue standards, and therefore the products concerned can be considered to comply with this criterion.

(g) Risks for public or animal health as regards the development of resistance

Anthelmintic resistance in food-producing animals

A number of experimental studies, review articles and conference papers attest to the existence of anthelmintic resistance in Ireland, and in other countries:

- Good *et al.*⁴¹ reported on studies carried out in sheep, which utilised a faecal egg count reduction test (FECRT) and a micro-agar larval development test (MALDT) to measure resistance to benzimidazole (BZ), levamisole (LV) and macrocyclic lactone (ML) anthelmintics in Irish commercial flocks between 2002 and 2010. The FECRT involves calculating the mean reduction in FEC at a specific time point following treatment with an anthelmintic in a sample of animals from a flock. The nematode population is considered resistant when the FECR is less than 95% and the lower 95% confidence limit is less than 90%. The principle of the MALDT is based on the development of larvae in the presence of varying concentrations of the anthelmintic. The FECRT results revealed that 88% of flocks and 39% of flocks were insensitive to BZ and LV, respectively. The MALDT assay indicated BZ resistance in 95% of flocks and LV resistance in 48% of flocks. A DrenchRite Assay was performed and this suggested that resistance to BZ, LM and ML in nematode populations was observed on 61%, 28% and 11% of farms, respectively.
- McMahan *et al.*⁴² reported that anthelmintic resistance was prevalent in Northern Irish sheep flocks. Treatment efficacy below 95%, indicating resistance, was detected in 81% of flocks

⁴¹ Good, B., Hanrahan, J.P., De Waal, T., Patten, T., Kinsella, A. and Lynch, C.O., 2012. Anthelmintic-resistant nematodes in Irish commercial sheep flocks – the state of play. *Irish Veterinary Journal*, 65:21.

⁴² McMahan, D., Bartley, D.J., Edgar, H.W.J., Ellison, S.E., Barley, J.P., Malone, F.E., Hanna, R.E.B., Brennan, G.P. and Fairweather, I., 2013. Anthelmintic resistance in Northern Ireland (I): Prevalence of resistance in ovine

tested for BZ resistance; in 14% of flocks tested for LV resistance and in 50% and 62% of flocks tested for ivermectin and milbemycin resistance, respectively. Monepantel resistance was absent in all flocks tested.

- Keegan *et al.*⁴³ confirmed the first report of ivermectin resistance in two Irish sheep farms, using both a FECRT as well as a controlled efficacy test. Parasite naïve lambs were artificially challenged with *Teladorsagia circumcincta* in order to test their sensitivity to BZ, LV and ivermectin by means of a FECRT. Both isolates were found to be resistant to all three anthelmintics with reductions of 47% (C.I. 10-68), 92% (C.I. 74-97) and 50% (C.I. 24-68) for the Farm A isolate and of 85% (C.I. 59-94), 89% (C.I. 69-96) and 73% (C.I. 49-86) for the Farm B isolate for BZ, LV and ivermectin, respectively.
- Keegan *et al.*⁴⁴ reported on a nationwide sheep technology adoption programme between 2013 and 2015 in which sheep farmers performed 4,211 drench tests and faecal egg counts over a 3-year period. Despite being the most common anthelmintic used, BZ treatment was found to be effective in only 31.5% of cases, with no reduction in FEC observed in 16% of cases. Efficacy of LV, ivermectins and moxidectin was reported to be 51.9%, 62.5% and 84% respectively.
- Sargison *et al.*⁴⁵ reported on an experimental study in sheep in Scotland in which a BZ-, LV- and ivermectin-resistant *T. circumcincta* worm population was treated with moxidectin orally. While treatment was effective in removing adult parasite burdens, the effect of the drug did not persist against resistant helminth populations.
- Mooney *et al.*⁴⁶ confirmed the existence of resistance in liver fluke to triclabendazole in an Irish sheep flock using a FECRT.
- Kamaludeen *et al.*⁴⁷ found reduced triclabendazole efficacy using a FECRT in 13 out of 21 sheep farms in the UK, with a complete lack of therapeutic efficacy observed on 9/26 farms. The authors advise that '*resistant genes have the potential to spread rapidly within and between populations of parasites affecting both sheep and cattle*'.
- From a survey of 34 sheep farms in the Netherlands, based on a FECRT, Ploeger and Everts⁴⁸ identified widespread resistance amongst gastrointestinal nematodes, with resistance to ivermectin, oxfendazole, closantel and moxidectin found in 78%, 73%, 60% and 47% of sheep flocks, respectively. Monepantel resistance was found in 8% of sheep flocks four years after introduction, while multi-drug resistance was present in more than half of the flocks. Of 22 flocks in which both MLs were tested, 18% showed no resistance against both drugs, 41%

gastrointestinal nematodes, as determined through faecal egg count reduction testing. *Veterinary Parasitology*, 195(1-2); 122.

⁴³ Keegan, J.D., Keane, O.M., Farrell, L., Byrne, W., De Waal, T., and Good, B., 2015. Characterisation of ivermectin and multi-drug resistance in two field isolates of *Teladorsagia circumcincta* from Irish sheep flocks. *Veterinary Parasitology: Regional Studies and Reports*, 3.

⁴⁴ Keegan, J.D., Keane, O.M., Good, B., De Waal, T., Denny, M., Hanrahan, J.P., Fitzgerald, W. and Sheehan, M., 2017. A nationwide survey of anthelmintic treatment failure on sheep farms in Ireland. *Irish Veterinary Journal*, 70;7.

⁴⁵ Sargison, N.D., Jackson, F., Bartley, D.J. and Moir, A.C.P. 2005, Failure of moxidectin to control benzimidazole-, levamisole- and ivermectin-resistant *Teladorsagia circumcincta* in a sheep flock. *Veterinary Record*, 156; 105.

⁴⁶ Mooney, L., Good, B., Hanrahan, J.P., Mulcahy, G. and De Waal, T., 2009. The comparative efficacy of four anthelmintics against a natural acquired *Fasciola hepatica* infection in hill sheep flock in the west of Ireland. *Veterinary Parasitology*, 164(2-4); 201.

⁴⁷ Kamaludeen, J., Graham-Brown, J., Stephens, N., Miller, J., Howell, A., Beesley, N.J., Hodgkinson, J., Learmount, J. and Williams, D., 2019. Lack of efficacy of triclabendazole against *Fasciola hepatica* is present on sheep farms in three regions of England, and Wales. *Veterinary Record*, 184(16); 1.

⁴⁸ Ploeger, H.W. and Everts, R.R., 2018. Alarming levels of anthelmintic resistance against gastrointestinal nematodes in sheep in the Netherlands. *Veterinary Parasitology*. 262: 11.

showed resistance against ivermectin only and 41% showed resistance against both MLs. No resistance was found to LV.

- O'Shaughnessy *et al.*⁴⁹ reported the first case of anthelmintic resistance in cattle in Ireland. In this study in two farms, calves that were naturally infested with populations of gastrointestinal nematodes were shown to be resistant to ivermectin following a FECRT.
- Kelleher *et al.*⁵⁰ demonstrated the presence of anthelmintic resistance to BZ and ML (ivermectin) in a survey of 16 Irish dairy calf-to-beef farms.
- O'Shaughnessy *et al.*⁵¹ reported ivermectin treatment failure on four Irish dairy farms. Using the FECRT to evaluate the performance of ivermectin in treating gastrointestinal nematode infections in first grazing season calves on four dairy farms in Co. Kilkenny, ivermectin-resistant nematodes were detected in all farms.
- Rose *et al.*⁵² conducted a systematic review of the literature and reported that anthelmintic resistance, assessed primarily using FECRTs, is widespread in ruminants in Europe, having been detected in all five gastrointestinal nematode genera and in 16 countries throughout Europe. Multiple drug resistance in three main genera infecting sheep and goats was reported in 10 countries.
- Geurden *et al.*⁵³ reported on a study of 753 animals on 40 farms in Germany (12 farms), the UK (10 farms), Italy (10 farms), and France (8 farms). Animals were selected based on pre-treatment faecal egg counts and were allocated to one of the two treatment groups. Each treatment group consisted of between 7 and 10 animals. A post-treatment faecal egg count was performed 14 days (± 2 days) after treatment. The observed percentage reduction was calculated for each treatment group based on the arithmetic mean faecal egg count before and after treatment. The resistance status was evaluated based on the reduction in arithmetic mean faecal egg count and both the lower and upper 95% confidence limits. A decreased efficacy was observed in half or more of the farms in Germany, France and the UK. For moxidectin, resistance was confirmed on three farms in France, and on 1 farm in Germany and the UK. For ivermectin, resistance was confirmed on three farms in the UK, and on 1 farm in Germany and France. The remaining farms with decreased efficacy were classified as having an inconclusive resistance status based on the available data.
- Tarbiat *et al.*⁵⁴ who investigated resistance in six commercial laying hen farms in Sweden reported that there is a lack of evidence of resistance to BZ in *Ascaridia galli*. They advised that more research was needed to confirm the results of the FECRT.

⁴⁹ O'Shaughnessy, J., Earley, B., Mee, J.F., Doherty, M.L., Crosson, P., Barrett, D., Prederville, R., Macrelli, M. and De Waal, T., 2014. Detection of anthelmintic resistance on two Irish beef research farms. *Veterinary Record*. 175; 120

⁵⁰ Kelleher, A., Keane, O. and Good, B., 2018. Anthelmintic resistance on dairy calf-to-beef farms in Ireland. *Teagasc AGRI.*, 13;2 https://www.teagasc.ie/media/website/publications/2018/TRResearch_Summer_2018-web-14.pdf Accessed on 10/06/2019.

⁵¹ O'Shaughnessy, J., Drought, Y., Lynch, J., Denny, M., Hurley, C., Byrne, W., Casey, M., De Waal, T. and Sheehan, M., 2019. Ivermectin treatment failure on four Irish dairy farms. *Irish Veterinary Journal*, 72; 4.

⁵² Rose, H., Rinaldi, L., Bosco, A., Mavrot, F., De Waal, T., Skuce, P., Charlier, J., Torgerson, P.R., Hertzberg, H., Hendrickx, G., Vercruyse, J. and Morgan, E.R., 2015. Widespread anthelmintic resistance in European farmed ruminants: a systematic review. *Veterinary Record*. 176(21); 546.

⁵³ Geurden, T., Chartier, C., Fankec, J., di Regalbonod, A.F., Traversa, D., von Samson-Himmelstjerna, G., Demeler, J., Vanimisetti, H., Bartram, D.J. and Denwood, M.J. 2015. Anthelmintic resistance to ivermectin and moxidectin in gastrointestinal nematodes of cattle in Europe. *International Journal for Parasitology: Drugs and Drug Resistance*, 5(3); 163.

⁵⁴ Tarbiat, B., Jansson, D.S., Tyden, E. and Hoglund, J. 2017, Evaluation of benzimidazole resistance in *Ascaridia galli*. *Parasitology*, 144(10); 1338.

- Kaplan⁵⁵ reported that suppressive anthelmintic treatment strategies that were originally designed to control *Strongylus vulgaris* in horses have inadvertently resulted in the selection of drug-resistant cyathostomins (Cyathostominae), which are now considered the principal parasitic pathogens of horses.
- Matthews⁵⁶ advised that BZ resistance is widespread globally in nematodes of horses. She reported that there are also many reports of BZ resistance as well as resistance to pyrantel in cyathostomins. Furthermore, reduced efficacy to ML compounds, principally measured as a reduction in strongyle egg reappearance time, was observed after treatment while ivermectin resistant, *Parascaris equorum*, an important pathogen of foals, was considered to be a further concern.
- Bottger⁵⁷ in her report to the EMA focus group meeting on anthelmintic resistance on 13 June 2016, charted the timelines for the recording of resistance to various anthelmintic classes in cattle, sheep and horses in Europe. The minutes of that meeting state that '*anthelmintic resistance is now present across all Europe, mostly in small ruminants*'⁵⁸. This meeting led to a revision of the EMA Reflection Paper on Anthelmintic Resistance⁵⁹. The reflection paper carries an overview of the resistance situation within the EU, which it states is an '*increasing problem worldwide, especially in ruminants and horses*'.

Conclusion on anthelmintic resistance

From the non-exhaustive scientific evidence, it is clear that anthelmintics that are intended for food-producing species cannot be considered to comply with this criterion.

Resistance to ectoparasitic drugs in food-producing animals

There are relatively fewer reviews or reports of resistance to ectoparasitic drugs in the published literature in Europe, compared to the situation for anthelmintics.

- Doherty *et al.*⁶⁰ reported resistance to MLs in sheep scab mites in four farms in the UK. *Psoroptes ovis* mites were collected from scab outbreaks in Wales and in England, from flock animals that had been treated previously with various injectable acaricides but had failed to respond to treatment and that showed persistent signs of *P. ovis* infestation. The authors opined that '*given the similarities in their mode of action as GABA (gamma-aminobutyric acid) agonists, stimulating the binding of neurotransmitter and inducing paralysis in arthropods and nematodes, it is highly likely that cross-resistance across the range of this class of compound will be detected*'.
- Lekimme *et al.*⁶¹ found that ivermectin was unable to control psoroptic mange (caused by *P. ovis*) in cattle during a clinical trial conducted during winter 2008/09 in Belgium. The authors

⁵⁵ Kaplan, R.M., 2002. Anthelmintic resistance in nematodes of horses. *Veterinary Research*. 33(5); 491.

⁵⁶ Matthews, J. B., 2014. Anthelmintic resistance in equine nematodes. *International Journal for Parasitology Drugs and Drug Resistance*, 4(3);310.

⁵⁷ Bottger, A., 2016. Anthelmintic resistance in Europe. Presentation to EMA Focus Group meeting on anthelmintic resistance. https://www.ema.europa.eu/en/documents/presentation/presentation-anthelmintic-resistance-europe-cattle-sheep-horses-anita-bottger_en.pdf . Accessed 12/06/2019.

⁵⁸ EMA Stakeholder Meeting – Minutes, Revision of the reflection paper on anthelmintic resistance. 22 June 2016. EMA/CVMP/EWP/573536/2013. https://www.ema.europa.eu/en/documents/minutes/minutes-veterinary-focus-group-meeting-stakeholders-revision-reflection-paper-anthelmintic_en.pdf. Accessed 12/06/2019.

⁵⁹ EMA Reflection paper on anthelmintic resistance, 21 April 2017. EMA/CVMP/EWP/573536/2013. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-anthelmintic-resistance_en-1.pdf. Accessed on 13/6/2019.

⁶⁰ Doherty E., Burgess S, Mitchell S, Wall R., 2018. First evidence of resistance to macrocyclic lactones in *Psoroptes ovis* sheep scab mites in the UK, *Veterinary Record*, 184(4); 106.

⁶¹ Lekimme, M., Farnir, F., Marechal, F. and Losson, B., 2010. Failure of injectable ivermectin to control psoroptic mange in cattle. *Veterinary Record*, 167(15); 575.

reported that 'the massive use of ivermectin and related compounds, often in suboptimal formulations such as pour-on and sustained release bolus products, is likely to be responsible for a marked selection pressure that could lead to resistance in psoroptic mites'.

- Sands *et al.*⁶² reported deltamethrin tolerance in cattle chewing lice *Bovicola bovis* in the UK. They speculated that, given the low concentrations of deltamethrin after pour-on or spot-on treatments in sites remote from the application site, and their findings of resistance, growing tolerance may exist in a large proportion of the UK *B. bovis* population.
- Coles⁶³, in a review article, cites the first case of pyrethroid-resistant sheep scab mites in the UK as far back as 1995, while the first case of organophosphate-resistant mites was reported from Scotland in 1996.
- Sevatdal *et al.*⁶⁴ reported on the results of monitoring of sea lice from fish farms in Norway, Scotland and Ireland. They concluded that reduced sensitivity to pyrethroids in these countries occurs occasionally.
- Aaen *et al.*⁶⁵ advised that the extensive use of medicinal treatment (organophosphates, pyrethroids, emamectin and benzoyl ureas) of farmed fish has resulted in drug-resistant sea lice occurring in farmed and possibly wild salmonids.
- Kaur *et al.*⁶⁶ observed that high levels of resistance in sea lice have developed to all chemicals used in salmon aquaculture. From her research on genotyping sea lice taken from the North Atlantic from the period 1998-2016, she concluded that the mechanism of resistance predates the introduction of organophosphates in salmon farming.
- Marangi *et al.*⁶⁷ reporting on a field survey of 7 naturally infested Italian caged laying poultry farms found that red mite populations were tolerant to carbaryl, permethrin or amitraz in six (86%), three (42%) and one (14%) of the farms respectively.
- Thomas *et al.*⁶⁸ reporting on the efficacy of fluralaner for the treatment of poultry red mite, *Dermanyssus gallinae* infestation in commercial poultry flocks in Europe, cited the emergence of resistance to carbamates, organophosphates, amidines, pyrethroids and spinosad as the reason for the development of the product.
- An EMA Draft Reflection Paper on Resistance in Ectoparasites⁶⁹ provides a useful overview of resistance in ticks, mites, lice, fleas, flies, mosquitoes, sand flies and sea lice against ectoparasitic substances that are used in veterinary medicines. The report states that 'structured

⁶² Sands, B., Ellse, L., Mitchell, S., Sargison, N.D. and Wall, R., 2015. First report of deltamethrin tolerance in the cattle chewing louse *Bovicola bovis* in the UK. *Veterinary Record*, 176(9); 231.

⁶³ Coles, G.C., 1998, Drug-resistant parasites of sheep; An emerging problem in Britain? *Parasitology Today*, 14(3); 86

⁶⁴ Sevatdal, S., Copley, L., Wallace, C., Jackson, D. and Horsberg, T.E., 2005. Monitoring of the sensitivity of sea lice (*Lepeophtheirus salmonis*) to pyrethroids in Norway, Ireland and Scotland using bioassays and probit modelling. *Aquaculture* 244(1); 19.

⁶⁵ Aaen, S.M., Helgesen, K.O., Bakke, J. M., Kaur, K. and Horsberg, T.E., 2015, Drug resistance in sea lice: a threat to salmonid aquaculture, *Trends in Parasitology*, 31(2); 72

⁶⁶ Kaur, K., Besnier, F., Glover, K.A., Nilsen, F., Aspehaug, V.T., Fjørtoft, H.B. and Horsberg, T.F., 2017, The mechanism (Phe362Tyr mutation) behind resistance in *Lepeophtheirus salmonis* pre-dates organophosphate use in salmon farming. *Scientific Reports*. 7(1); 12349.

⁶⁷ Marangi, M., Cafiero, M.A., Capelli, G., Camarda, A., Sparagano, O.A.E. and Giangaspero, A., 2009. Evaluation of the poultry red mite, *Dermanyssus gallinae* (Acari: Dermanyssidae) susceptibility to some acaricide in field populations from Italy. *Experimental and Applied Acarology*; 48(1); 11.

⁶⁸ Thomas, E., Chiquet, M., Sander, B., Zschiesche, E. and Flochlay, A. S., 2017. Field efficacy and safety of fluralaner solution for administration in drinking water for the treatment of poultry red mite (*Dermanyssus gallinae*) infestations in commercial flocks in Europe. *Parasites & Vectors*. 10(1); 457.

⁶⁹ EMA Draft Reflection paper on resistance in ectoparasites, 13 September 2018, EMA/CVMP/EWP/310225/2014. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-resistance-ectoparasites_en.pdf Accessed 13/06/2019.

resistance surveillance programs are only available in very few EU Member States, and only for specific parasites’.

- A report from an EMA workshop on veterinary medicines for bees⁷⁰ referred to widespread resistance in the Varroa mite in Europe. The findings are also supported by studies conducted in Ireland, which reported resistance to pyrethroids⁷¹.

Conclusion on ectoparasitic resistance

From the non-exhaustive scientific evidence and despite the lack of documented research information from Ireland (apart from data on bees), it is clear that resistance to ectoparasitic drugs is present in many animal species across Europe. Ectoparasitic drugs that are intended for food-producing species cannot, therefore, be considered to comply with this criterion.

Resistance to anti-coccidial veterinary medicines

Coccidia are single-celled obligate intracellular parasites that can infect mammals, poultry and fish. There are relatively few reports of drug resistance in coccidia in Europe, compared to the literature regarding helminth resistance:

- Odden *et al.*⁷² reported coccidial resistance in Norwegian sheep farms. They performed a control efficacy trial to monitor ovine *Eimeria* spp. resistance to toltrazuril. Twenty lambs were artificially infected with field isolates of 100,000 *Eimeria* spp. oocysts, and randomly assigned to a 20 mg/kg toltrazuril or physiological saline treatment groups. No significant difference was observed in faecal score, growth, gross pathology or histological changes between the two groups. Oocyst excretion was monitored in all lambs from day 14 onwards. Toltrazuril efficacy was measured using the faecal oocyst count reduction test (FOCRT). Toltrazuril treatment did not result in a significant reduction in oocyst excretion in the treated animals, compared with the controls. Additionally, no significant differences were observed in clinical presentation, gross pathology, and histopathological findings. Speciation data revealed multiple non-pathogenic and pathogenic species were resistant to the drug. *E. ovinoitalis* was the dominant species excreted from infected lambs.
- Toltrazuril resistance was confirmed experimentally in a field isolate of *Cystoisospora suis* in piglets in Austria, by Shrestha *et al.*⁷³ In a controlled study, groups of 5 to 8 piglets were infected either with a Holland strain of *C. suis* that had been isolated from a Dutch pig herd where lack of efficacy to toltrazuril had been observed, or a toltrazuril susceptible strain of *C. suis*, (Wien). Following this, the piglets were randomly assigned to control, 20 mg/kg bodyweight of toltrazuril, or 30 mg/kg bodyweight of toltrazuril in the Holland strain group or to control or 20 mg/kg body weight of toltrazuril in the Wien strain group. Faecal excretion of *C. suis* oocysts was completely suppressed by the toltrazuril treatment in group Wien, whereas every single piglet infected with the Holland isolate shed oocysts regardless of the toltrazuril dose. Diarrhoea was not observed in toltrazuril Wien group, all other groups developed increased mean faecal scores after infection and showed appreciable levels of diarrhoea. The authors concluded that

⁷⁰ EMA Workshop on medicines for bees – What the Agency can do to increase availability. 14-15 December 2009, Report, 19 March 2010, EMA/28057/2010. https://www.ema.europa.eu/en/documents/other/workshop-medicines-bees-report_en.pdf. Accessed 28/06/2019.

⁷¹ Coffey, M.F. and Breen, J. 2011, Detection of pyrethroid resistant mites in Ireland, *Mellifera*, 11 (21/22); 20.

⁷² Odden, A., Enemark, H.L., Ruiz, A., Robertson, L.J., Ersdal, C., Nes, S.K., Tømmerberg, V. and Stuen, S., 2018. Controlled efficacy trial confirming toltrazuril resistance in a field isolate of ovine *Eimeria* spp. *Parasites & Vectors*, 11(1): 394.

⁷³ Shrestha, A., Freudenschuss, B., Jansen, R., Hinney, B., Rutkowski, B. and Joachim, A., 2017.

Experimentally confirmed toltrazuril resistance in a field isolate of *Cystoisospora suis*. *Parasites & Vectors*, 10(1); .317.

this indicated enteritis as a consequence of parasite replication and unresponsiveness to treatment.

- Skampardonis *et al.*⁷⁴ investigated the efficacy of toltrazuril treatment against isoporiasis in pigs under field conditions in Greece. The authors noted that extensive application of the drug over 10 years has led to isolated cases of resistance being reported. However, in the trial conducted, the authors reported that in piglets treated with toltrazuril at the dose rate of 20 mg/kg body weight, orally administered on the third day after birth, treatment delayed the onset of oocyst excretion and decreased the odds of diarrhoea occurring.
- Stephan *et al.*⁷⁵ found that resistance among field isolates of *Eimeria* in ten broiler farms to coccidiostats was widespread in a study conducted in Germany in 1997. Many of the strains showed multiple resistance to monensin, salinomycin, nicarbazin, halofuginone, robenidine, toltrazuril and diclazuril.
- Williams⁷⁶ reported on a study of the emergence of resistance in six British broiler farms that were sampled in 1968-1969. The commercial performance of the first 3–5 crops of broilers that were medicated with decoquinate on each farm was monitored, supplemented by assessments of the species, population dynamics and decoquinate-resistance of coccidia isolated from each farm. During the rearing of each flock in a single shed on each farm, oocysts were counted in fresh faecal samples collected on three occasions, and the species were identified by their morphology if possible, supported if necessary, by the biological characteristics of infections in chickens. It was concluded that inherently resistant mutants of *E. acervulina*, *E. brunetti*, *E. maxima*, *E. tenella*, and probably also *E. mitis* and *E. praecox*, were selected from field populations by 6 weeks during their first exposure to decoquinate, although no impact on bird health was observed.
- In a review article, Abbas *et al.*⁷⁷ reported that resistance in *Eimeria* to all anti-coccidial drugs used in poultry has been described in different parts of the world. The authors opined that this was because of their extensive use. They advised that new drugs should be developed to replace the older ones against which resistance has developed, however '*it takes a long time to develop any new compound*'. Peek and Landman⁷⁸ reported that in some cases resistance to anti-coccidial drugs could be induced very quickly, as in the case of quinolones and pyridinols, while in other cases it could take several years for resistance to emerge.

Conclusion on coccidial resistance

From the non-exhaustive scientific evidence and despite the lack of research information from Ireland, it is clear that resistance is present in coccidia of many animal species in the EU. Therefore, the availability of anti-coccidial drugs that are intended for food-producing species through licensed merchant outlets cannot be considered to comply with this criterion.

Overall conclusion on risk of development of resistance to antiparasitic veterinary medicinal products

From the available scientific evidence, it is clear that the antiparasitic veterinary medicines that are intended for food-producing species cannot be considered to comply with this criterion. Risks of

⁷⁴ Skampardonis, V., Sotiraki, S., Kostoulas, P. and Leontides, L., 2010, Effect of toltrazuril treatment in nursing piglets naturally infected with *Isoospora suis*. *Veterinary Parasitology*, 172; 46.

⁷⁵ Stephan, B., Rommel, M., Dauschies, A. and Haberkorn, A., 1997. Studies of resistance to anticoccidials in *Eimeria* field isolates and pure *Eimeria* strains. *Veterinary Parasitology*, 69(1); 19

⁷⁶ Williams, R.B., 2006, Tracing the emergence of drug-resistance in coccidian (*Eimeria* spp.) of commercial broiler flocks medicated with decoquinate for the first time in the United Kingdom. *Veterinary Parasitology*, 135(1); 1.

⁷⁷ Abbas, R.Z., Iqbal, Z., Blake, D., Khan, M.N. and Saleemi, M.K., 2011. Anticoccidial drug resistance in fowl coccidia: the state of play revisited. *World's Poultry Science Journal*, 67; 337.

⁷⁸ Peek, H.W. and Landman, W.J.M., 2011, Coccidiosis in poultry: anticoccidial products, vaccines and other preventative strategies, *Veterinary Quarterly*, 31(3); 143.

resistance have been identified with the use of anthelmintic products, ectoparasitic products, and anti-coccidial products, across many animal species. Resistance to anthelmintics has been confirmed and is now widespread in livestock and other species in Ireland. Resistance to ectoparasitic and anti-coccidial drugs appears not to be monitored currently in Ireland, but the available evidence from countries with similar farming conditions to Ireland (e.g. UK and other EU countries) is that resistance has also developed.

CHAPTER THREE: THE SUPPLY OF VETERINARY MEDICINAL PRODUCTS FOR FOOD-PRODUCING ANIMALS IN IRELAND, AND OTHER EUROPEAN COUNTRIES

3.1 Current situation regarding the supply classification in Ireland

Most veterinary medicines containing antiparasitic substances are currently supplied in Ireland as non-prescription medicines. However, a limited number are supplied as prescription medicines and some anti-coccidial veterinary medicinal products are available both as prescription as well as non-prescription medicines. Most of the products that are currently authorised contain active substances that have been available in Ireland for three or more decades and which were originally authorised as non-prescription veterinary medicines. For products containing new active substances that were authorised within the last seven years, most remain currently authorised as requiring a prescription, save for a number of anti-coccidial medicines where some are prescription medicines and some are not.

Following their assessment by the national competent authority (now known as the HPRA) at the time of original authorisation, the majority of anthelmintics and ectoparasitic medicines were categorised for supply under a 'Licensed Merchant' (LM) category. This means that they may be sold without a veterinary prescription by outlets which are licensed by DAFM. There are few antiparasitic veterinary medicines restricted to prescription control currently:

- Two anthelmintics that were authorised for sheep. One contains derquantel plus abamectin (Startect) and the second contains monepantel (Zolvix). Both products contained a new active substance at the time of original authorisation (and therefore were subject to mandatory prescription control), but both have now been authorised for at least five years,
- One antiparasitic drug, imidocarb (Imizol), to control babesiosis (Redwater) in cattle. Redwater is a serious and potentially fatal disease in cattle, and the diagnosis and treatment requires professional judgment.
- Three anthelmintics containing flubendazole or fenbendazole that are used for in-feed or in-water use in pigs and poultry. In accordance with EU legislation⁷⁹ medicated feedingstuffs for in-feed administration can only be supplied under veterinary prescription.
- One ectoparasitic medicine containing permethrin for horses (Z-itch). Permethrin is authorised for sport horses, which are not allowed for human consumption. Accordingly, the product has a restricted use (exceptional use for treatment of sport horses where no other authorised medicine is available) and the veterinarian who treats the animal must record this treatment in the animal's passport.
- A number of endectocides containing ivermectin that are given as premixes for medicated feed of pigs. In accordance with EU legislation, medicated feedingstuffs can only be supplied under prescription.
- A cutaneous spray containing phoxim (ByeMite) for hens. At the time of original authorisation, the product contained a new active substance which was, therefore, subject to mandatory prescription control.
- Two ectoparasitic medicines for fish (Amx containing deltamethrin and Slice containing emamectin). At the time of original authorisation, the products contained a new active substance which was, therefore, subject to mandatory prescription control.
- Several anti-coccidial drugs for use in livestock and poultry. At the time of original authorisation, the products contained a new active substance which was, therefore, subject to mandatory prescription control. In some cases, an applicant has successfully applied in recent years to vary the marketing authorisation on the basis of evidence of safe use of the product. Note that in contrast to veterinary medicines containing coccidiostats that are used to treat or prevent disease, certain anti-coccidial drugs that are used to improve the animals' performance and health are regulated as feed additives⁸⁰. Feed additives are regulated by DAFM and are outside the scope of this review.

⁷⁹ Directive 90/167/EEC on medicated feedingstuffs

⁸⁰ Regulation (EC) No 1831/2003

Medicines authorised by the HPRA for animals that have a designated route of supply of 'LM' (Licensed Merchant) may be purchased from internet sites or by mail order but only where the supplier is specifically licensed by DAFM.

In respect of veterinary medicines authorised centrally in the European Union, these may be supplied throughout the Community. In this case, the European Commission establishes the appropriate method of supply. It is noteworthy that all antiparasitic veterinary medicinal products that have been authorised by the EU Commission for use in food-producing species, with the exception of those authorised for bees, are restricted to supply under veterinary prescription. These products include anthelmintics (monepantel, fenbendazole), ectoparasitic drugs (fluralaner) and anti-coccidial drugs (toltrazuril and halofuginone). Whether a product is authorised nationally or centrally, the allocation of an appropriate category of supply is based on an evaluation of the risks involved and taking account of the available legal categories which are defined by national and European legislation. The method allocated is subject to review based on the experience gained through use of the product in the field and on any change in the benefit: risk profile.

Certain coccidiostats are authorised for use in poultry in Ireland as feed additives, by DAFM. These products are for oral use in healthy birds. Certain other anti-coccidial drugs are authorised by the HPRA for use as veterinary medicinal products to treat or prevent disease in animals and poultry.

Beekeeping has grown in popularity in Ireland over the last number of years as a hobby, with the average beekeeper maintaining 3 hives. To the knowledge of the TF, there is little or no veterinary involvement in the beekeeping sector in Ireland currently. There are six products licensed for use in bees in Ireland, and these are all licensed as treatments for the varroa mite which is endemic in honey bee populations. Research trials have been carried out in Ireland which show resistance to some of the older licensed treatments in the past. There have been three new products licensed for use in bees against varroa in the last 5 years. All ectoparasitic products for bees are available without veterinary prescription. The three veterinary medicinal products for bees that have been authorised centrally by the EU Commission within the last 3 years have been judged by the CVMP to comply with the criteria in Directive 2006/130/EC.

3.2 Position of products in other EU Member States

Following a survey on Member States (MSs) that was undertaken in April and May 2019, of 27 countries that responded, all advised that antiparasitic veterinary medicinal products for food-producing species were mainly or exclusively restricted to veterinary prescription. In respect of the answers received, the following qualifications were noted:

- a) In the UK, anthelmintics and ectoparasitic medicines may also be prescribed and supplied by suitably qualified persons (SQPs) in addition to prescribing by veterinarians. SQPs must undertake a study module in animal diseases and drug supply in respect of the particular species of interest to them and must pass an exam before they can prescribe veterinary medicinal products that are classified for supply under this route. The SQP is permitted to prescribe only for the species for which s/he has successfully completed the study module.
- b) In Malta, some anthelmintic and ectoparasitic medicines are available without prescription; the legal provisions are under review currently.
- c) In France, once a veterinary prescription is written the antiparasitic products concerned can be dispensed by a veterinarian or pharmacist that is associated with an approved breeder association.
- d) In Belgium, some anthelmintics for horses may be supplied without prescription. Other anthelmintics for food-producing animals can only be supplied under veterinary prescription.
- e) In Sweden, veterinary medicines are supplied under veterinary prescription through pharmacies, including on-line pharmacies.

- f) In Denmark, anthelmintic drugs are available only under prescription, but are prohibited for routine prophylactic treatment⁸¹.

Article 105 of Regulation 2019/6 states that an exemption which allows non-veterinarians to prescribe a veterinary medicine is restricted to only those MSs which had this provision in force at the date of entry into force of the regulation. As this regimen existed only in the UK at the time of adoption of the Regulation in January 2019, the exemption cannot now be used in Ireland or any of the other MS of the EU.

Of 16 MSs which provided additional information on the period of validity of a veterinary prescription, the duration appears to vary widely from 10 days (Lithuania) to indefinitely (Bulgaria and Cyprus), with several countries having a period of 3 months or less (Hungary, Latvia, Croatia, Spain, Estonia, Czech, and Belgium).

3.3 Developing trends in agriculture, veterinary medicinal products and animal diseases

Between 2010 and 2017, the volume of farm outputs in Ireland rose by 21 percent, mainly as a result of expansion of milk outputs⁸². Farm profitability is reported⁸³ as highly variable, with average income for dairy farms, beef farms and sheep farms reported for 2018 being €61,446, €14,560 and €13,297 respectively, and in the case of beef and sheep farming, direct farm payments from the EU under the Common Agricultural Policy accounting for the vast majority of this income. The national dairy herd is expanding at the same time as the national suckler herd is declining. The effect of a hard Brexit is forecast to be highly negative for Irish agricultural production and income. In the medium term, it seems that given the very low margins experienced in the beef and sheep sectors, continued consolidation of these sectors seems inevitable. Changes in parasite burden on farms is expected to occur as a result of changes in the type of farming being undertaken.

Climate change is expected to play an increasing role in changing the expression and distribution of parasitic diseases in Ireland⁸⁴ and in other countries⁸⁵. Moreover, increased animal density in grazing animals is expected to compound the challenge. Genomic research programmes to identify and breed animals with less susceptibility to parasites are being developed but progress is likely to be slow due to the low heritability of resistance in animals⁸⁶. While awaiting the future elaboration of genetically resistant host species⁸⁷, nematode control *has evolved to a more logical manipulation of host-parasite*

⁸¹ Nielsen, M.K., Monrad, J. and Olsen, S.N., 2006. Prescription-only anthelmintics – A questionnaire survey of strategies for surveillance and control of equine strongyles in Denmark. *Veterinary Parasitology*, 135: 47

⁸² Irish Agriculture: Economic Impact and Current Challenges, 2018, T. Conefrey. [https://www.centralbank.ie/docs/default-source/publications/economic-letters/vol-2018-no.8-irish-agriculture-economic-impact-and-current-challenges-\(conefrey\).pdf?sfvrsn=6](https://www.centralbank.ie/docs/default-source/publications/economic-letters/vol-2018-no.8-irish-agriculture-economic-impact-and-current-challenges-(conefrey).pdf?sfvrsn=6), accessed on 24/05/2019.

⁸³ Teagasc National Farm Survey 2018, https://www.teagasc.ie/media/website/publications/2019/NFS-2018_final_web.pdf Accessed 20/08/2019.

⁸⁴ Thompson, R.C.A., 1999, *Veterinary Parasitology: Looking to the next millennium*. *Parasitology Today*, 15(8); 320.

⁸⁵ Emery, D.L., Hunt, P.W. and Le Jambre, L.F., 2016. *Haemonchus contortus*: the then and now, and where to from here? *International Journal for Parasitology*, 46(12); 755.

⁸⁶ Twomey, A.J., Sayers, R.G., Carroll, R.I., Byrne, N., O'Brien, E., Doherty, M.L., McClure, J.C., Graham, D.A. and Berry, D.P., 2016. Genetic parameters for both a liver damage phenotype caused by *Fasciola hepatica* and antibody response to *Fasciola hepatica* phenotype in dairy and beef cattle. *Journal of Animal Science*. 94; 4109.

⁸⁷ Waller, P.J., 2006, From discovery to development: Current industry perspectives for the development of novel methods of helminth control in livestock. *Veterinary Parasitology*, 139; 1.

*equilibrium in grazing systems*⁸⁸. Morgan *et al*⁸⁹ opined that anthelmintic resistance is threatening the sustainability of livestock production, especially in grazing systems, while, at the same time, changes in weather and climate are making infection patterns less predictable. This means that '*fixed protocol-driven approaches to helminth control are less reliable*'. In their review, the authors advise that the side effects of anthelmintic use, including the impact on the environment and on non-target fauna needs to be better understood. They also advise that the direct cost of anthelmintic resistance includes:

- The cost of the drugs used,
- The associated labour costs in administering it, and
- The reduction in animal performance and farm sustainability.

They advise that the evolution of anthelmintic resistance is driven by a range of factors, including intrinsic factors (drug- and species-specific susceptibility, parasite population size, genetic variability) and external factors (treatment frequency and intensity, size of refugia etc.). In their view, optimal usage of anthelmintics in the face of resistance needed to be tailor-made to the individual farm and should consider selection pressure and grazing management approaches.

Vercruysse *et al*,⁹⁰ advised of two trends for the future of helminth control in grazing ruminants:

- a) Breeding programmes would strive for the identification of optimal animal phenotypes, which are more resilient and resistant to helminth infections. New diagnostic technologies and interpretation of live information streams would allow for more rational control practices, such that anthelmintic treatment would become a remedy for individual under-performing animals rather than a blind whole-group management routine. This would reduce the selection pressure for resistance.
- b) Increased demand for animal protein, coupled with a drive for greenhouse gas reduction would drive animal production efficiency. This would be likely to have different implications depending on the production systems in different countries, but anthelmintic treatment could remain necessary provided it would not be undone by accelerating the development of anthelmintic resistance.

Another issue is that even though some diagnostics are available to detect certain parasites in livestock, they are not always sufficiently discriminatory (to be able to identify the precise parasite involved), or cost-effective. Moreover, private laboratories conducting the diagnostic tests might not always be accredited. Furthermore, diagnostic tests are not available to detect most parasites that are present in animals during the pre-patent period or to measure pasture parasite burdens. Diagnostic bulk milk tank samples may not detect individual positive animals, or antibody levels may remain high for long periods post treatment with an effective antiparasitic drug⁹¹.

Against a background of changing farming conditions is the increasing contraction of the veterinary pharmaceutical industry that is taking place globally over recent times. This level of consolidation results in reduced research into discovery of new antiparasitic drugs and fewer new products being

⁸⁸ Zvinorova, P.I., Halimani, T.E., Muchadeyi, F.C, Matika, O., Riggio, V. and Dzama, K., 2016. Breeding for resistance to gastrointestinal nematodes – the potential in low-input/output small ruminant production systems. *Veterinary Parasitology*, 225; 19.

⁸⁹ Morgan, .E.R., Aziz, N.A., Blanchard, A., Charlier, J., Charvet, C., Claerebout, E., Geldhof, P., Greer A.W., Hertzberg, H., Hodgkinson, J., Höglund, J., Hoste, H., Kaplan, R.M., Martínez-Valladares, M., Mitchell, S., Ploeger, H.W., Rinaldi, L., von Samson-Himmelstjerna, G., Sotiraki, S., Schnyder, M., Skuce, P., Bartley, D., Kenyon, F., Thamsborg, S.M., Vineer, H.R., de Waal, T., Williams, A.R., van Wyk, J.A. and Vercruysse, J., 2019, 100 Questions in livestock helminthology research. *Trends in Parasitology*, 35(1); 52.

⁹⁰ Vercruysse, J., Charlier, J., Van Dijk, J., Morgan, E. R., Geary, T., Von Samson-Himmelstjerna, G., and Claerebout, E. (2018). Control of helminth ruminant infections by 2030. *Parasitology*. 145(13); 1655.

⁹¹ Gilmore, J., 2016. The role of the veterinary laboratory in achieving and maintaining improved herd health. *Veterinary Ireland Journal*, 6(5): 279.

developed⁹². This situation means that new drugs are unlikely to become available to meet the developing resistance of parasites, so more needs to be done to preserve their efficacy into the future.

Given the context of impending and significant change in food production and farming practices due to Brexit, climate change and global trade issues, the TF is not in a position to pronounce on how the landscape for existing suppliers of veterinary medicinal products will be affected. Moreover, such a judgment will be strongly influenced by national legislation on how the prescription regimen for veterinary medicines will be established and monitored.

3.4 Future developments affecting veterinary medicinal products as a result of Regulation 2019/6

The control of resistance is one of the objectives of Regulation 2019/6, including both antimicrobial resistance (AMR) as well as antiparasitic resistance. The regulation applies to all products, whether centrally authorised or nationally authorised. Although there are a range of specific provisions directed to enhancing the available regulatory tools to control AMR, a number of measures have also been provided to address antiparasitic resistance, including:

- a) Article 4: The assessment of the benefit-risk balance now specifically addresses *'any risk relating to the development of resistance'* in addition to the risks relating to the quality, safety and efficacy of the product,
- b) Article 35: The SPC must contain information relating to *'special conditions for use, including restrictions on the use of antiparasitic veterinary medicinal products in order to limit the risk of development of resistance'*,
- c) Article 37: An application for a marketing authorisation must be refused where *'the risk for antiparasitic resistance outweighs the benefits of the veterinary medicinal product to animal health'*,
- d) Article 141: The CVMP has a task to *'provide scientific advice on the use of antiparasitics in animals in order to minimise the occurrence of resistance in the Union, and update that advice when needed'*.

The technical requirements for application dossiers have also been enhanced with regard to testing to investigate resistance.

In accordance with the new legislation, following its application in 2022, the text of the packaging and labelling of veterinary medicinal products is to be rationalised, in order to reduce the textual information that is provided and to use standardised pictograms and abbreviations throughout the EU. This is expected to be a positive development insofar as it should facilitate the use of multilingual packaging across the EU.

According to Articles 10 and 11 of Regulation 2019/6, the information that will be allowed on the immediate and outer packaging of veterinary medicinal products is more limited than that currently used. This means that precise information on dosing instructions might not be allowed on the immediate and outer packaging of veterinary medicines, (however, these instructions can be included in the package leaflet). Many product labels for food-producing animals currently carry a table that indicates the dose rate of the product for particular live weight bands of the animals concerned. These dose rates are an easily accessible source of dose-rate information for farmers that can help reduce miscalculation of the dose rates and the risk of under-dosing. The moving of these tables to a package leaflet that might or might not be supplied with the product (it is possible that the leaflet might be made available electronically) is expected to make this information less readily accessible.

Moreover, information on the method of supply might not be allowed on the immediate or outer packaging (Member States can include an 'identification code', but this is considered to refer to the marketing authorisation number or code). Additional information concerning distribution, possession

⁹² Woods, D.J. and Knauer, C.S., 2010. Discovery of veterinary antiparasitic agents in the 21st Century: A view from industry. *International Journal for Parasitology*, 40: 1177.

or other direction may be given in the package leaflet. This means that in contrast to the situation today, in future the labels and outer packaging of veterinary medicinal products might not identify the authorised method of supply of the product to the end-user or purchaser.

3.5 Requirement of Regulation 2019/4

Regulation 2019/4, which comes into effect in January 2022, requires that medicated feed can only be supplied on foot of a veterinary prescription⁹³. This is not expected to result in any change to the current system, as anthelmintics that are supplied as authorised veterinary premixes currently require a veterinary prescription while their incorporation into finished feeds also requires a veterinary written direction.

⁹³ Article 16 of Regulation 2019/4

CHAPTER FOUR: STAKEHOLDER CONSULTATION, ANALYSIS OF BENEFITS AND RISKS OF MAINTAINING THE *STATUS QUO*, OPTIONS FOR CHANGE, IMPACT AND LOGISTICS

4.1 Introduction

The objective of this chapter is to consider the merits of the current and possible new system for control of antiparasitic veterinary medicinal products used in food-producing animals, to address the challenges identified and to consider the perspective of stakeholders.

4.2 Stakeholder consultation

A stakeholder consultation was undertaken between 20 May 2019 and 21 June 2019. The consultation took two forms:

- a) An electronic email survey to 122 marketing authorisation holder (MAH) recipients as well as 30 individual recipients from Irish farming organisations, veterinary organisations, species organisations, government bodies, representative parties and agriculture lobby groups. The MAHs were selected by the HPRA based on regulatory contact in relation to veterinary medicines previously. The list of interested parties was chosen either by the HPRA or identified by members of the TF as being likely to be interested parties. The email used provided an on-line link to a survey where recipients were invited to address what they considered to be the likely benefits and risks both of maintaining the current regulatory supply channels for antiparasitic veterinary medicines in food-producing animals as well as the benefits and risks of restricting the products concerned to prescription control. In addition, the recipients were invited to make any related observations on the topic and on any transition to a new system of control.
- b) An invitation within the survey email to the recipients to provide a written and detailed submission with any supporting evidence in relation to the system for the supply of antiparasitic veterinary medicinal products that are intended for food-producing animals.

Of the 39 respondents to the on-line survey, not all respondents addressed every question. Moreover, in at least three cases there seemed to be a degree of coordination between the respondents, as evidenced by the very similar structure and language used in the answers. Although the survey was anonymous, in a number of cases the respondents self-identified themselves as representing a stakeholder organisation, and the answers provided were consistent with, and language used in them was the same or essentially similar to those provided in the written submissions by the organisations concerned. Some eight respondents provided a more detailed written submission.

4.3 Stakeholder views on maintenance of the *status quo*

An analysis of responses showed that they were divided on the merits of maintaining the status quo. Some 20 respondents considered that the current system has several benefits:

- Competitive pricing of products,
- Wide product choice from a variety of outlets, that are located throughout the country,
- Ease and timeliness of access to products by farmers,
- Traceability of products used,
- Low levels of residues in analysed food samples,
- Products are available in licensed merchants by a trained, 'Responsible Person'. These individuals have access to a wide range of resources provided by MAHs and other bodies to maximise the quality of advice available to farmers,
- The potential for retailers and MAHs to 'take ownership of knowledge transfer' of best practice of antiparasitic medicines on farms [to educate end-users],
- Maintaining the current system would avoid the need to establish new systems and to [have to] educate users and prescribers accordingly.

One respondent quoted levels of compliance from monitoring of foodstuffs under the National Residue Control Plan reports from 2010 to 2017 as evidence for the high standard of traceability. The same

respondent cited a reference by Charlier *et al.*⁹⁴ who advised that economic factors are not the sole driver of animal health decisions on farms. These authors advise that several diagnostic tools and methods are now available to assess the economic impact of helminth infections on dairy cattle farms, and they recommend that anthelmintics should be used on the basis of relevant diagnostic tests to prove the need and efficacy of treatment and to guide decision-making in the case of resistance.

In contrast to those who believed the current system had positive attributes, twenty-eight respondents cited the continuing development of anthelmintic resistance as an expected risk of the current system of supply, as well as a risk to consumers from residues due to misuse. One respondent opined that the products concerned were being supplied '*as commodities*' and that '*worming programmes [were] not planned in the majority of cases, but decided on price and non-scientific advice*'. Other respondents considered that there are risks not only of resistance but also regarding environmental risks, especially with long-acting anthelmintics. Others considered that an inadequate appreciation of how pour-on formulations should be properly administered could lead to under-dosing due to animal grooming. Other respondents opined that a significant proportion of farmers currently receive poor or no professional advice when purchasing antiparasitic products in licensed merchant outlets and that there was poor understanding of rotation of anthelmintic drug classes or the epidemiology of the parasites involved. Some felt that the current system propagated uninformed use, overuse and misuse as profit margins at licensed merchant retailers were lower than those available to veterinary practitioners. One respondent considered the low price of antiparasitic veterinary medicines as one of the drivers of drug misuse '*the fact that a farmer can treat a 500 kg animal for 50 cents with an ivermectin results in widespread and indiscriminate use of these products*'. Some felt that resistance would ultimately lead to reduced production efficiency on Irish farms as well as reduced welfare standards and a decline in overall farm profitability. One respondent opined that there was a risk that if the current system was maintained, resistance levels would continue to increase until the threshold was reached where the problem could no longer be properly addressed.

4.4 Stakeholder views on possible changes to the supply classification

Twenty-seven respondents to the survey foresaw potential benefits associated with restricting antiparasitic veterinary medicines to prescription control as:

- Reducing the risk of inappropriate or unnecessary use,
- Reducing antiparasitic resistance,
- Improving the quality of advice and implementation of best practices and health programmes on-farm,
- Improving the standard of care of animals, where the correct dosage and drug substance is given,
- Reducing the risk of misuse due to a lack of knowledge about differential diagnoses amongst farmers regarding other possible causes of ill thrift and diarrhoea,
- Enabling better recording of product supply, thereby facilitating better monitoring and research,
- Compliance with the relevant EU legislation on the supply of veterinary medicinal products that are used for food-producing species.

By contrast, twenty-six respondents perceived possible risks with restricting antiparasitic veterinary medicine to prescription control. The main risks identified were:

- Reduction in competition, leading to increased prices in the cost of medicines. It was stated that currently only 26% of the products are supplied through vet practice channels and removing the products from LM outlets would lead to increased cost and inconvenience for farmers. It could also create a vested interest for the prescriber or anti-competition

⁹⁴ Charlier, J., De Waele, V., Ducheyne, E., Van Der Voort, M., Vande Velde, F. and Claerebout, E. 2016. Decision making on helminths in cattle: diagnostics, economics and human behaviour. *Irish Veterinary Journal*. 69; 14.

practices by vets who might promote the product having the highest margin rather than the most appropriate one,

- Less frequent worming of animals leading to animal welfare issues, as farmers would wait until a visit by a veterinary practitioner rather than paying separately for a veterinary prescription,
- Diseased animals or bees being left untreated,
- Sub-clinical infestations becoming established with consequential impact on animal productivity,
- Reduction in the number of products available, and possibly also in the number of retail outlets supplying the products,
- Development of a black market or on-line purchase, as farmer buyer groups or individual users, would access medicines outside the State illegally,
- There might be a lack of sufficient numbers of veterinary practitioners in certain rural areas, thereby hampering access by farmers,
- Corporate veterinary practices or 'motorway vets' supplying product without advice,
- Resistance to change by farmers, as such a decision is expected to be politically and commercially unpopular to vested interests,
- Reduction in employment opportunities for Responsible Persons, with a negative effect on the rural economy,
- Use of ineffective alternative feed supplements that carried claims for parasite control,
- Farmers might 'abdicate responsibility for mitigating the risk of anthelmintic resistance' to the prescribing veterinarian.

One of the respondents drew a parallel in relation to factors that influence prescribing behaviours of veterinary practitioners in cattle practice in Ireland when prescribing antibiotics. In a peer-reviewed paper cited by the respondent, Gibbons *et al.*⁹⁵ found that non-clinical issues, including issues related to professional stress, influenced the prescribing decision of the majority of veterinarians. The respondent opined that *'there is no reason to assume that a similar pattern would not arise for the prescribing of antiparasitic medicines if this was their sole route of supply'*.

Eight respondents foresaw no risks with implementing restrictions. One respondent considered that *'veterinary practitioners ... operate at much longer opening hours so access to medicines would not be compromised'*. Another pointed out that veterinary practices are *'present in every rural town in Ireland'* and antiparasitic products on sale there were as competitive as other retail outlets. Yet another pointed out that the products concerned were already restricted to veterinary prescription in other EU countries and this was evidence of the feasibility of such a system in Ireland.

Although one respondent to the consultation stated that only 26% of antiparasitic veterinary medicinal products are supplied by veterinary practices, publicly-available information from an independent consultancy service provider⁹⁶ shows that 57% of all veterinary medicinal products supplied in Ireland in 2012 were sourced from veterinary practices, with only 19% and 14% sourced from merchants and co-ops respectively. Moreover, that report shows that veterinary practices play an increasing role in the supply of veterinary medicines in Ireland, compared to the position a decade earlier.

One respondent advised that restricting the supply of antiparasitic products to veterinary prescription-control would not change current practices in parasitic control that favour the development of resistance, such as 'dose-and-move' and preventative blanket treatment. Noteworthy in one of the responses was the statement that *'neither the LM nor the POM system can prevent improper anthelmintic*

⁹⁵ Gibbons, J.F., Boland, F., Buckley, J.F., Butler, F., Egan, J., Fanning, S., Markey, B.K. and Leonard, F.C., 2012, Influences on antimicrobial prescribing behaviour of veterinary practitioners in cattle practice in Ireland. *Veterinary Record* 172; 14.

⁹⁶ Roche, D., 2012. Republic of Ireland animal medicines review, July 2012 data. <https://iasis.ie/Documents/Denise%20Roche%20for%20website.pdf> Accessed 19/07/2019.

use'. Ultimately, it was pointed out that it would be the farmer who administered the product, so it was his/her responsibility to ensure correct use. Other respondents felt that although the current system met farmer needs overall there was an opportunity to improve it. Another respondent considered that without the introduction of a diagnostic prerequisite for the prescribing of antiparasitic veterinary medicines, a change in the supply of these products would be unlikely to achieve any benefit in reducing the development of antiparasitic resistance. It was suggested by another respondent that the ideal system was one based on diagnostic results in conjunction with relevant advice on parasite management and preventative grazing strategies. One respondent considered that if it would be deemed necessary to introduce the need for a veterinary prescription for antiparasitic treatments then all such prescriptions should be made on the basis of defined empirical data and the broadest possible number of distribution channels should be maintained. They advised that the current numbers of responsible persons should be maintained in order to ensure farmer access to timely treatment, choice of products and cost-effectiveness.

This point of view was supported by another respondent, which cited a published paper by Becher *et al.*⁹⁷, who surveyed equine parasite control programmes by horse owners in five different countries. The authors found that Danish participants used more faecal analyses and treated horses less often than those in the USA, Germany, Austria and the Netherlands. They concluded that the differences in parasite control methods between countries could not be adequately explained by differences in legislative controls in the route of supply of anthelmintics, (albeit that the Netherlands introduced prescription only rules in the relatively recent past [2008] and German legislation allowed for a herd-based approach to parasite control compared to the situation in Denmark, where the authorities generally required individual diagnostics). The authors also noted that cultural differences, differences in knowledge amongst horse owners as well as the cost of faecal egg counts in the different countries could also play a part.

Another respondent advised that in any new system education should play a crucial role and that *'the lack of a formal reaccreditation/continuous education system means that the knowledge level of responsible persons [in licensed merchant outlets] may vary, which could lead to inappropriate/outdated advice being given'*.

One respondent expressed concern that given the poor profitability of livestock farming in Ireland, farmers had extremely limited capacity to absorb veterinary prescription costs. S/he advised that animal health and welfare might be negatively impacted due to reluctance/failure to treat or manage parasites due to increased cost. The respondent advised that the predominantly Spring calving/lambing, pasture-based system of production has the potential to lead to high exposure to nematode and trematode parasites and parasite control plans and strategies to mitigate the risk of anthelmintic resistance should take into account the unique production systems and selection pressures in this country. It was proposed that an all-industry approach to *'co-design a solution from the bottom up'* would be the appropriate action to address this challenge. Such a multi-actor approach was considered as making any new control system more accessible to farmers and as helping the mind-set of farmers by enabling co-ownership of the developed solutions.

One respondent stated that a multi-actor approach comprising farmers, Teagasc, veterinary practitioners and other stakeholders could address current problems in sustainable parasite control such as inconsistent advice and could identify drivers and constraints to sustainable parasite control and hence influence change effectively. The respondent advised that the livestock sector in Ireland is highly fragmented and recommended a coordinated and combined national partnership approach to enable collective action. The respondent also considered that there is a need to upskill all vendors, veterinary

⁹⁷ Becher, A. M., van Doorn, D.C., Pfister, K., Kaplan, R.M., Reist, M. and Nielsen, M.K., 2018., Equine parasite control and the role of national legislation - A multinational questionnaire survey. *Veterinary Parasitology* 259; 6

professionals and advisers in sustainable anthelmintic usage combined with regular retraining/CPD. The same respondent is of the opinion that this could be undertaken within the existing supply framework, and cited a report by Easton *et al*,⁹⁸ which reported that in the UK (where a different regulatory system is in place) knowledge of basic helminthology, best practice guides in anthelmintic use for livestock and horses, and relevant dispensing legislation was of an equivalent level both amongst veterinary practitioners and amongst non-veterinary staff who had received appropriate training.

None of the respondents considered specific risks other than those relating to anthelmintic resistance. This may signal that the potential adverse effects of the products concerned on the environment are unknown to them as of now, or they do not believe that this is a likely risk.

4.5 Analysis and impact assessment by Task Force

As reviewed in Chapter Two, the available scientific evidence shows that antiparasitic veterinary medicines that are intended for use in food-producing species do not comply with the criteria for derogation from veterinary prescription specified in Regulation 2019/6. It is the opinion of the TF that a consequence of this determination is that in order to comply with Regulation 2019/6 any products that are supplied without prescription currently must be changed from the current method of supply to supply under veterinary prescription.

It is beyond the scope of this document to carry out an impact assessment of the economic effects of changing the method of supply to veterinary prescription in respect of antiparasitic veterinary medicinal products for food-producing animals. Indeed, such modelling would be expected to be complex as it would have to consider the effects both on the economics of farm production, as well as on those of persons who are engaged in trade in antiparasitic veterinary medicinal products. In this regard it is noteworthy that LM products can currently be supplied at a distance e.g. by persons licensed by DAFM to supply antiparasitic veterinary medicinal products over the internet. However, products that are classified as prescription-only medicines cannot be supplied in this manner.

Antiparasitic resistance is a problem not only in Ireland but globally, including in countries where such products have been subject to prescription control for many years. Regarding the available literature, Kaplan⁹⁹ proposed that *'anyone intending to deliver an anthelmintic agent should address a long list of questions before the proper drug [could] be selected, including the following:*

- *Which species of parasite are the most important to control in the type and age class of the animals of interest?*
- *Which stages of those parasites are most likely to be present?*
- *Which drugs (or drug classes) provide the proper spectrum of activity against the parasite species and the stages being targeted?*
- *What are the host-parasite dynamics that are most relevant to the control of those species?*
- *Which animals in the herd require anthelmintic treatment, and which do not?*
- *Are those drugs still effective against the particular parasite species or stages being targeted at this site (or are the parasites resistant to that drug or class of drugs)?*

Kaplan advocated restricting the use of anthelmintic drugs for control of parasites of livestock and opined that *'putting veterinarians in the driver's seat, by restricting anthelmintics to prescription use, [was] the single best step towards achieving [an immediate impact to slow the tide of resistance]'*. He reported that in Denmark, some five years after the enactment of national legislation to restrict anthelmintics to prescription-control, Danish equine veterinarians demonstrated *'a dramatic change in practices and had become heavily involved in parasite-control programmes. Parasite surveillance and drug efficacy testing [was] now the new normal, and the result [had] been a more-than-50-percent decrease in the frequency*

⁹⁸ Easton, S., Bartley, D.J., Hotchkiss, E., Hodgkinson, J.E., Pinchbeck, G.L., Matthews, J.B., 2016. Use of a multiple choice questionnaire to assess UK prescribing channels' knowledge of helminthology and best practice surrounding anthelmintic use in livestock and horses. *Preventative Veterinary Medicine*. 128; 70.

⁹⁹ Kaplan, R.M., 2013, Prescription-only anthelmintic drugs: the time is now. *BioScience*, 63(11); 852.

of anthelmintic treatment, with no concomitant increase in the diagnosis of parasitic disease in Danish horses’.

Van Wyk *et al.*¹⁰⁰ advised that the ‘conventional paradigm of chemical-based parasite control must be changed, from one of maximum to one of optimal worm management compatible with sustainability’. The authors advised that sustainable integrated parasite management solutions and refugia-based approaches were more complex than whole-herd/flock treatments in conventional programmes, and were poorly understood and adopted by farmers. O’Shaughnessy *et al.*¹⁰¹ identified practical difficulties under Irish conditions in the use of targeted selective treatments (TST) of dairy calves where only individual animals were treated. They advised that the use of live weight gain alone as a TST measure might not be suitable, while FEC were not a reliable guide to the parasitic burden of a calf, and plasma pepsinogen measurement might also not always be a reliable diagnostic. In a longitudinal study over 3 years in sheep in the UK to compare the effects of traditional and the UK’s sustainable control of nematode parasites in sheep (SCOPS) initiative, Learmount *et al.*¹⁰² found that SCOPS farms carried out significantly fewer anthelmintic treatments per year, and used fewer anthelmintic doses/animal than traditional farms while achieving the same lamb productivity. They advised that ‘although [the] results suggest some economic benefit for those farmers in the SCOPS group, a full cost-benefit analysis would need to also account for the resource effort incurred in using other SCOPS procedures such as FECs, required in order to target treatments’.

Charlier *et al.*¹⁰³ advised that infection pressure with gastrointestinal nematodes varies throughout the year as a function of weather and farm management. They pointed out that control programmes needed to be re-evaluated and adapted regularly to maintain their efficacy in the face of climate change and farm management. Moreover, they opined that devising new control programmes would be a complex task as they would have to take ‘into account effects of multiple interactions on parasite populations [including gastrointestinal nematodes, lungworms, protozoa and trematodes], which might be conflicting and different for each worm species’. The authors report that an important limitation for the development and validation of targeted selective treatment strategies, as well as associated epidemiological models, is the lack of validated tools to quantify the parasite population on pasture. They advise that each specific treatment strategy must be adjusted to local farming conditions. They highlight the challenge of defining the combination of diagnostic markers that could be used for identification of the individual animals or groups of animals requiring treatment, the need to determine treatment thresholds as well as the need for effective knowledge transfer to end-users.

In their reflection paper on anthelmintic resistance⁵⁹, the CVMP stressed that measures to reduce the need of anthelmintics and to promote the appropriate use of the drugs were important to delay resistance development. The CVMP gave examples of prudent use advice:

- To base treatment on confirmation of worm burdens or solid epidemiological information,
- To employ targeted selective treatment approaches at farm level,
- To avoid routine and frequent use,

¹⁰⁰ Van Wyk, J.A., Hoste, H., Kaplan, R.M. and Besier, R.B. 2006. Targeted selective treatment for worm management – How do we sell rational programs to farmers? *Veterinary Parasitology*, 139(4); 336.

¹⁰¹ O’Shaughnessy, J., Earley, B., Mee, J.F., Doherty, M.L., Crosson, P., Barrett, D. and De Waal, T., 2015. Controlling nematodes in dairy calves using targeted selective treatments. *Veterinary Parasitology*, 209 (3-4); 221.

¹⁰² Learmount, J., Stephens, N., Boughtflower, V., Barrecheuren, A., Rickell, K., Massei, G. and Taylor, M., 2016. Three-year evaluation of best practice guidelines for nematode control on commercial sheep farms in the UK. *Veterinary Parasitology*. 226; 116.

¹⁰³ Charlier, J., Thamsborg, S. M., Bartley, D. J., Skuce, P. J., Kenyon, F., Geurden, T., Hoste, H., Williams, A. R., Sotiraki, S., Höglund, J., Chartier, C., Geldhof, P., van Dijk, J., Rinaldi, L., Morgan, E. R., von Samson-Himmelstjerna, G., Vercruyse, J. and Claerebout, E., 2017. Mind the gaps in research on the control of gastrointestinal nematodes of farmed ruminants and pigs. *Transboundary and Emerging Diseases*, 65(S1); 217.

- To dose correctly and particularly to avoid under-dosing,
- To manage pastures properly and to maintain an appropriate level of refugia, in particular by keeping a part of the herd untreated.

Acknowledging that there is a lack of knowledge on the current situation of ectoparasite resistance in Europe, the CVMP/EMA⁶⁹ advised that *'action requiring professional expertise and input from other parties is needed to improve understanding, monitoring, management practices, and the prudent use of ectoparasiticides so as to reduce inappropriate use and consequently delay resistance development'*. The CVMP/EMA also advised that *'prescription-only status is recommended for ectoparasiticides for food-producing animals to avoid inappropriate use'*.

Previous experience in changes to controls in the supply of veterinary medicinal products

The current routes of sale of veterinary medicines that are supplied in Ireland were established already in 1996¹⁰⁴. Despite many revisions to the animal remedies legislation since then, up to now, there has not been any real effort to consider the merits of changing the supply routes of antiparasitic medicines, even if the supply routes for certain antibacterial medicines and vaccines have been changed during this period. The TF considered that it would be useful to take into account previous experience in changing the way veterinary products have been supplied nationally in order to consider the impact of any possible future changes.

At the request of the Minister for Agriculture and Food, the Irish Medicines Board (IMB) produced a report on the method of supply of intramammary antibiotics in 1999¹⁰⁵. The report examined the sale and supply of the products involved, which were available for self-selection by farmers from licensed co-operative societies as well as from pharmacies and veterinary practitioners previously. The report recommended a change to a new control system requiring a veterinary prescription, but recognised that any change to the *'legislative controls on the supply of intramammary antibacterials should be adequately flagged in advance to all parties concerned and would become legally operational after a transition period to be determined by the Minister'*. The foreseen restrictions on supply were not welcomed in all quarters and were found to be politically difficult¹⁰⁶. In the event, the Department of Agriculture and Food did not sanction the change to prescription control until 8 June 2006¹⁰⁷, some seven years later. Indeed that change was not finally implemented on the ground until 1 July 2007¹⁰⁸ due to the logistics involved in amending the marketing authorisations and producing the associated labelling changes. Even this period was followed by a grace period of six months where the Department agreed not to uplift non-compliant stock from the market and where the regulations were amended to allow the products concerned to be dispensed by licensed merchants under prescription¹⁰⁹.

¹⁰⁴ SI No. 179/1996, <http://www.irishstatutebook.ie/eli/1996/si/179/made/en/print> Accessed on 2.05.2019

¹⁰⁵ Report of the IMB on the availability of intramammary products, 22.09.1999, <https://www.hpra.ie/homepage/veterinary/safety-information/safety-notices/item?t=/report-of-the-imb-to-the-minister-for-agriculture-food-on-the-availability-of-intramammary-products&id=49d3f825-9782-6eee-9b55-ff00008c97d0>, as referred to in address to Joint Committee on Agriculture and Food, 22.01.2003. https://www.oireachtas.ie/ga/debates/debate/joint_committee_on_agriculture_and_food/2003-01-22/2/ Accessed on 2.05.2019

¹⁰⁶ See address to Joint Committee on Agriculture and Food, 22.01.2003. https://www.oireachtas.ie/ga/debates/debate/joint_committee_on_agriculture_and_food/2003-01-22/2/ Accessed on 2.05.2019

¹⁰⁷ Correspondence on file at HPRA

¹⁰⁸ IMB Newsletter No 24, April-July 2006, <https://www.hpra.ie/docs/default-source/publications-forms/newsletters/imb-newsletter-issue-no-24-april-july-2006.pdf?sfvrsn=2> Accessed on 2.05.2019

¹⁰⁹ SI 786 of 2007.

More recently, in 2007 the IMB produced a report¹¹⁰ on the allocation of an appropriate method of supply category in respect of veterinary vaccines that were authorised nationally. Although some changes to the categorisation of individual vaccines were made, the overall number of products affected was not great. The change process was undertaken following dialogue between the IMB and the companies involved. Recognising that some of the products concerned had a seasonal cycle, the IMB decided that all packaging and literature for vaccines that required amendment should comply with the new policy by 30 June 2009¹¹¹, thereby giving companies more than 18 months to make the necessary changes.

4.6 Perspectives of stakeholders on logistics of any change

Based on the replies to the survey questionnaire during the stakeholder consultation, stakeholders had mixed views on the time needed to transition to a new system. Ten respondents felt that any change should be carried out as quickly as possible, or within two years given the increasing risk of anthelmintic resistance, risk of stockpiling by farmers and/or political reaction. Seven respondents considered that the implementation should be carried out on a phased basis over a period of years. Six felt that the time needed would depend on how long it took to carry out the necessary communications and training, while three considered it would depend on how long it took out to roll out infrastructure to support the diagnostic tests and herd health programmes needed to support evidence-based prescriptions. Three respondents advised that MAHs would need time to make the necessary changes to their product labelling, and that period would determine how long was needed. Three others considered that the existing role of licensed merchants needed to be considered in the evolution of any new system.

One stakeholder considered that whatever the outcome of the review, specific thought and provision needed to be made for antiparasitic medicines for honey bees.

4.7 Perspective of Task Force on logistics of any change

The HPRA is the competent authority for the authorisation of veterinary medicinal products in Ireland and is free to decide the timelines for implementation. The opinion of the TF is that the maximum period of time until the date of implementation of Regulation 2019/6 on 28 January 2022 should be set. This period of time is expected to:

- a) Provide DAFM with sufficient time to consider whether a change to national prescribing legislation is needed to complement the requirements of Regulation 2019/6, and to give effect to that legislation,
- b) Provide notice to veterinary practitioners, health care professionals, farmers and users that the supply of antiparasitic products is being changed,
- c) Provide diagnostic service providers and agricultural advisors time to adapt their infrastructure, if needed,
- d) Provide sufficient notice to licensed merchants so that they can adjust their businesses accordingly,
- e) Provide MAHs with sufficient time to change the product labelling.
- f) Allow for any consultation necessary between regulatory authorities (i.e. DAFM and the HPRA) and the relevant stakeholders in the implementation of this report.

Policy options

A consequence of the finding that antiparasitic veterinary medicinal products that are intended for use in food-producing species do not comply with all the criteria for derogation from veterinary prescription specified in Regulation 2019/6, and presuming agreement of the HPRA with the analysis of the TF, is that the HPRA will need to engage with MAHs to ensure the implementation of the required changes

¹¹⁰ Report of the IMB on the classification of methods of supply of veterinary vaccines. 28.11.2007. <https://www.hpra.ie/docs/default-source/default-document-library/report-of-imb-working-group-on-the-classification-of-methods-of-supply-for-veterinary-vaccines.pdf?sfvrsn=2> Accessed on 2.05.2019.

¹¹¹ IMB Newsletter No 28, September – December 2007, <https://www.hpra.ie/docs/default-source/publications-forms/newsletters/imb-newsletter-issue-no-28-september-december-2007.pdf?sfvrsn=2> Accessed on 2.05.2019.

to the supply classification for any products that have previously been supplied without a veterinary prescription. However, the precise mechanism for the operation of the regulatory and legal framework underpinning the operation of the prescription (including dispensing) is a matter for DAFM in the first instance.

The TF expects that this report will be published at the end of 2019, following its consideration by the ACVM and the Authority of the HPRA. Publication is expected to allow DAFM a period of time before the implementation of the Regulation 2019/6 in January 2022 to consider various policy options for changes to national legislation and the conditions surrounding the writing and dispensing of a veterinary prescription. This proactive risk-management approach is preferable to that of a reactive one, such as might occur, for example, following an audit by the EU Commission to evaluate national compliance with the regulatory and control measures concerning veterinary medicinal products. Indeed the TF noted that a previous audit conducted by the Food and Veterinary Office in 2003¹¹² had identified failings in compliance with prescription requirements for certain products authorised nationally which necessitated immediate remedial actions.

In accordance with Article 105(4) of Regulation 2019/6 a veterinary prescription can be issued only by a veterinary practitioner, meaning that a prescription system akin to the retail supply of anthelmintics by SQPs as exists in the UK is not available to Irish legislators. However, a number of policy options are available that could nuance how the retail system could best operate in Ireland while remaining compliant with the requirements for retail sale. An impact assessment of policy options on resistance control as well as on stakeholders and current product providers would be needed. The options should place the control of resistance as its central aim and consider:

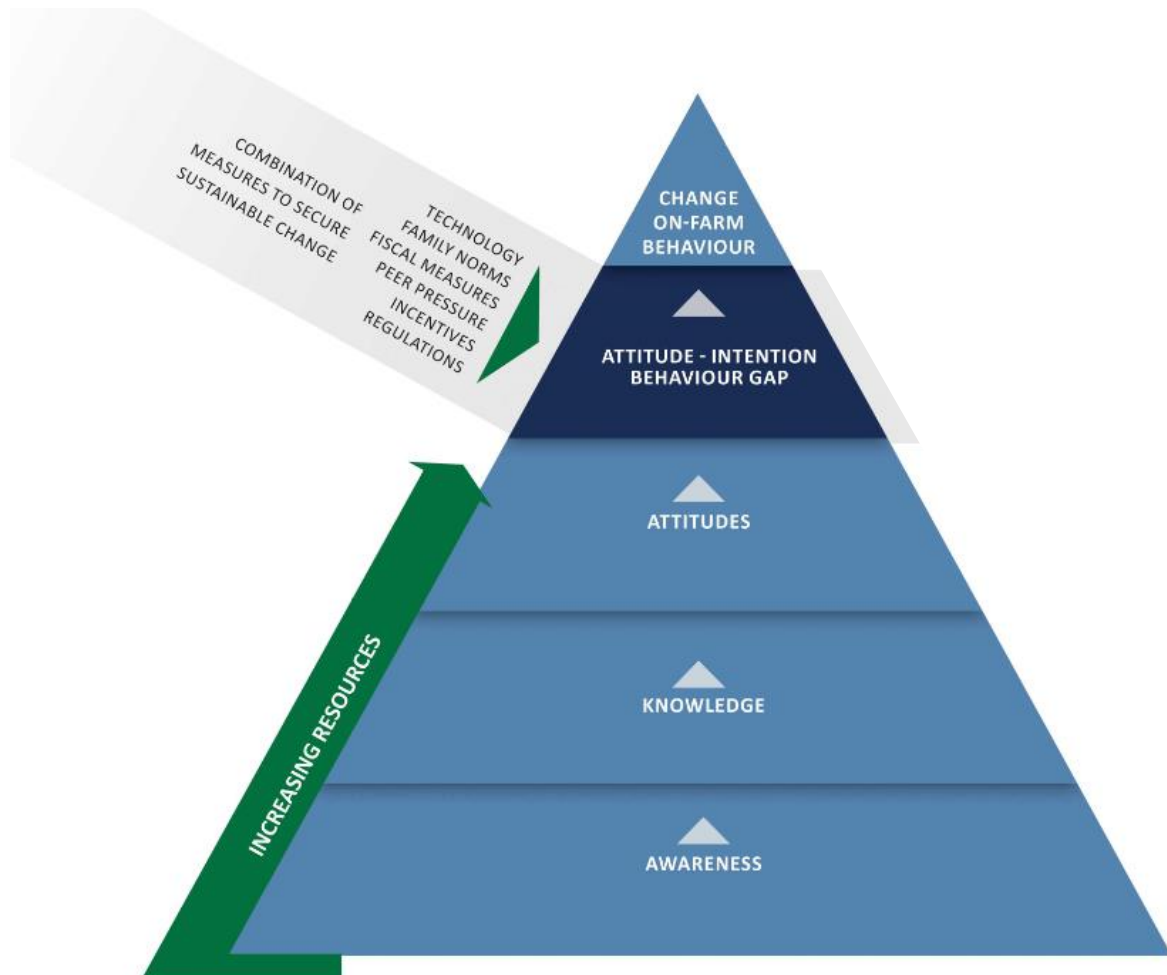
- What changes in the national legislation are required to ensure that antiparasitic veterinary medicinal products that are designated veterinary prescription control are accessible in a manner which:
 - a. Limits the development of resistance,
 - b. Fosters sustainability of the drugs used,
 - c. Promotes the use of evidence-based scientific tests to underpin the use of the drugs,
 - d. Provides for the necessary control and access, and,
 - e. Complies with Regulation 2019/6.
- Whether there would be any limitations or conditions for veterinary practitioners or other prescribers that would restrict their rights or ability to prescribe the products in question. This might include specification of the detailed conditions for issuing a prescription, as well as the operation of any specified animal health and welfare programmes for the farm/animal etc.,
- What limitations or conditions, if any, should attach to those authorised to dispense veterinary prescriptions for antiparasitic veterinary medicinal products,
- Whether a particular provision is necessary for antiparasitic veterinary medicines for bees, poultry, fish and minor species,
- Whether any changes to the legislation governing the purchase and possession of the relevant animal remedies and associated record-keeping would be needed,
- Whether, or to what extent, existing actors in the provision of antiparasitic diagnostic services to food-producing animals would be actively engaged in discussions on the preceding policy options.

On the question of stakeholder involvement in the development of policy, Garforth¹¹³, based on research conducted in the UK, advised that many farmers view government departments and agencies as ill-informed about the realities farmers face and were principally interested in regulating and

¹¹² DG (SANCO)/9049/2003 – MR Final, Report of a mission carried out in Ireland from 20 to 24 October 2003 in order to evaluate the control of residues in live animals and animal products. http://ec.europa.eu/food/audits-analysis/act_getPDF.cfm?PDF_ID=3669 . Accessed 17/07/2019.

¹¹³ Garforth, C., 2015, Livestock keepers' reasons for doing and not doing things which governments, vets and scientists would like them to do. *Zoonoses and Public Health*, 62; 29.

restricting what farmers could do. He advised that farmers' decisions are influenced by their values, attitudes and the view of people and institutions whose expertise and opinions they respect. The TF was informed about a model for change in farmer behaviour regarding disease management (Figure 1): Figure 1. Model for change in farmer behaviour regarding disease management (based on, and adapted, from the model provided by Animal Health Ireland).



This model is in keeping with the views of Ritter *et al*¹¹⁴, who advised that '*farmers will make management decisions based on their unique circumstances, agricultural contexts, beliefs, and goals... Approaches that appeal to farmers' internal motivators or that unconsciously elicit the desired behaviour will increase the success of the intervention*'.

¹¹⁴ Ritter, C., Jansen, J., Roche, S., Kelton, D.F., Adams, C.L., Orsel, K., Erskine, R.J., Benedictus, G., Lam, T.J.G.M. and Barkema, H.W., 2017. *Invited review: Determinants of farmers' adoption of management-based strategies for infectious disease prevention and control.* Journal of Dairy Science, 100(5); 3329

CHAPTER FIVE: CONCLUSIONS, RECOMMENDATIONS AND DATA GAPS

5.1 Conclusions

Having reviewed the detailed scientific evidence for antiparasitic veterinary medicinal products from the perspective of the criteria established by Regulation 2019/6, the TF has concluded that:

- Noting that veterinary medicines are medicinal products that carry a level of risk, overall there is evidence of compliance with the instructions of use of antiparasitic products. As a general remark the TF deduces from the evidence of usage of antiparasitic veterinary medicinal products over recent decades that farmers and product users possess the necessary skill to administer the pharmaceutical forms of the products concerned, albeit that the knowledge relating to parasitology and best practice in use of antiparasitic veterinary medicines is not evenly distributed amongst stakeholders. Therefore, the products concerned can be considered to comply with this criterion.
- There is some evidence that anthelmintic and ectoparasitic veterinary medicinal products present a direct or indirect risk, if administered incorrectly. Risks have been identified in regard to environmental safety, as well as for user safety. Therefore, antiparasitic veterinary medicines that are intended for food-producing species cannot be considered to comply with this criterion in the strict sense. Evidence concerning environmental risks of anti-coccidial drugs is sparse.
- Noting that all veterinary medicinal products carry comprehensive instructions, including precautions and warnings regarding use, there is limited evidence that the products concerned contain warnings of potentially serious adverse events deriving from their correct use. Therefore, the products concerned can be considered to comply with this criterion.
- Noting that there are legal obligations regarding the reporting of suspected adverse reactions to veterinary medicinal products, there is limited evidence that the products concerned have been the subject of adverse event reporting. However, the evidence is that such events are infrequent particularly given the wide use of the products concerned. Therefore antiparasitic veterinary medicinal products can be considered to comply with this criterion,
- Noting that all veterinary medicinal products carry comprehensive instructions, including precautions and contraindications, there is no evidence that the products concerned contain specific contraindications to other veterinary medicinal products that are commonly used without veterinary prescription (in combination or otherwise). Therefore, the products concerned can be considered to comply with this criterion.
- Noting that all veterinary medicinal products carry risks for public health as regards residues where the withdrawal period is not correctly observed or where product administration has not followed precisely the instructions for use or in other rare circumstances, the available scientific evidence from the results of national residue monitoring plans undertaken by the State demonstrate that isolated cases of residue violations involving anthelmintic and ectoparasitic veterinary medicinal products have been reported each year. However, given the widespread use of the products concerned over many years and the excellent record of compliance with the food residue standards, antiparasitic veterinary medicinal products can be considered to comply with this criterion,
- There is robust scientific evidence of widespread resistance to anthelmintics in parasites of livestock in Ireland. Therefore, antiparasitic veterinary medicines that are intended for food-producing species cannot be considered to comply with this criterion
- There is robust scientific evidence of anthelmintic resistance in parasites of other food-producing species, including reports from European countries with similar farming and animal husbandry conditions to those in Ireland. Therefore, antiparasitic veterinary medicines that are intended for food-producing species cannot be considered to comply with this criterion.

- There is robust scientific evidence of resistance in ectoparasites to several veterinary drug classes, including reports from European countries with similar farming and animal husbandry conditions to those in Ireland. Therefore, antiparasitic veterinary medicines that are intended for food-producing species cannot be considered to comply with this criterion.
- There is robust scientific evidence of resistance to anti-coccidial veterinary medicinal products, including reports from European countries with similar farming and animal husbandry conditions to those in Ireland. Therefore, antiparasitic veterinary medicines that are intended for food-producing species cannot be considered to comply with this criterion.

Accordingly, having reviewed all available evidence, the TF concludes that antiparasitic veterinary medicinal products 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.

5.2 Recommendations

- a) The available scientific evidence shows that antiparasitic veterinary medicines that are intended for use in food-producing species do not comply with the criteria for derogation from veterinary prescription specified in Regulation 2019/6. A consequence of this determination is that any such products that are supplied without veterinary prescription would need to be upregulated to supply under veterinary prescription. The TF recommends that the Authority of the HPRA carefully consider this recommendation.
- b) The TF recommends 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.
- c) The TF recommends that those involved in the prescribing and dispensing of antiparasitic veterinary medicinal products are provided with access to training/CPD on sustainable parasite control.
- d) Given that a number of policy options have been identified in this report regarding the development of an appropriate regulatory framework for the supply of antiparasitic veterinary medicinal products that are designated veterinary prescription control, it is recommended that DAFM carefully considers the merits of the various options.
- e) Given the expression of interest by certain stakeholders in providing parasitological diagnostic services to farmers, it is recommended that DAFM consider elaborating the system for veterinary prescription of antiparasitic medicines which support evidence-based prescribing.
- f) Given the known rationalisation of the text of the labelling and outer packaging of veterinary medicinal products that will take place from January 2022 as a consequence of Regulation 2019/6, there is a need for MAHs and other stakeholders to consider how best to disseminate the specific information on dose banding and instructions for use of antiparasitic veterinary medicinal products to the end-users.
- g) In the event that the Authority accepts the conclusions of this report, there will be a need for existing stakeholders to adapt to the requirement for a veterinary prescription for antiparasitic veterinary medicinal products. It is recommended that the HPRA provides the maximum flexibility and allows a period until 1 January 2022 to comply with this report. It is also recommended that stakeholders, including veterinarians, other health care professionals and licensed merchants be informed of this report in order to be able to engage with DAFM in relation to the elaboration and implementation of any new regulatory framework.
- h) Given the status of the honey bee and its importance in pollination, it is recommended that special status be given to antiparasitic veterinary medicinal products that are indicated for bees (in line with that applying to centrally authorised products for bees).

5.3 Data gaps

- a) There appears to be a lack of research or survey monitoring data in Ireland on resistance for ectoparasites, liver fluke and coccidia.
- b) There appears to be a deficit in the monitoring of drugs used in antiparasitic veterinary medicinal products in the environment, apart from limited research on bees.

ENDS

Appendix 1: Classification criteria for veterinary medicinal products intended for use in food-producing animals that may be exempted from the requirement for veterinary prescription [extract from Article 34 of Regulation (EU) 2019/6]

- a. The administration of the veterinary medicinal product is restricted to pharmaceutical forms requiring no particular knowledge or skill in using the products;
- b. The veterinary medicinal product does not present a direct or indirect risk, even if administered incorrectly, to the animal or animals treated or to other animals, to the person administering it or to the environment;
- c. The summary of product characteristics of the veterinary medicinal product does not contain any warnings of potentially serious adverse events deriving from its correct use;
- d. Neither the veterinary medicinal product nor any other product containing the active substance has previously been the subject of frequent adverse event reporting;
- e. The summary of product characteristics does not refer to contra-indications related to the use of the product concerned in combination with other veterinary medicinal products commonly used without prescription;
- f. There is no risk for public health as regards residues in food obtained from treated animals even where the veterinary medicinal product is used incorrectly;
- g. There is no risk to public or animal health as regards the development of resistance to substances even where the veterinary medicinal product containing those substances is used incorrectly.

Appendix 2: Terms of reference of the Task Force on Method of Supply of antiparasitic veterinary medicinal products that are indicated for food-producing animals

Objective: To review the current methods of supply of antiparasitic veterinary medicinal products that are authorised by the HPRA for food-producing animals as not requiring prescription control and to produce a report on their suitability against the criteria established by Regulation (EU) 2019/6/EU. For the purposes of this review, antiparasitic veterinary medicinal products includes anthelmintics, ectoparasitic products and veterinary medicinal products containing coccidiostats.

The report should provide advice to the ACVM, and consider:

1. The scientific evidence available,
2. The criteria set out in Article 34 of Regulation (EU) 2019/6,
3. The practical experience in the supply of antiparasitic veterinary medicinal products for food-producing animals that do not require a prescription in Ireland currently,
4. If relevant, the position on such products in other EU Member States,
5. Developing trends in agriculture, veterinary medicines or animal diseases and how these might be influenced by the current and future supply methods,
6. The likely risks, if any, associated with maintaining the current regulatory regimen,
7. The likely impact of any change of method of supply, in terms of ensuring the quality, safety and efficacy of use of the medicine, as well as its impact on animal health and welfare, and on stakeholders,
8. If a change to the existing method of supply is considered warranted, to outline how best that change should be made (timeframe, logistics etc.),
9. To consider any other relevant facts it deems appropriate to compile this report.

Appendix 3. Regulatory controls on the supply of veterinary medicines in Ireland

Allocating the route of supply of a veterinary medicinal product

The legal framework that governs the route of supply of veterinary medicines in Ireland is set out in national legislation¹¹⁵. The categories of supply are set out below in table 1.

Table 1. The categories of supply of veterinary medicinal products in Ireland, and their associated meaning

SYMBOL	ROUTE OF SUPPLY	ASSOCIATED MEANING
VPO 1	Veterinary Practitioner use only	For use by veterinary practitioners only
VPO	Veterinary Practitioner use only	For use by veterinary practitioners only
POM	Prescription only medicine	For use under the prescription of a veterinary practitioner
POM(E)	Prescription only medicine exempt	For supply by veterinary practitioners or pharmacists (in person) only
PS	Pharmacy only	For supply by veterinary practitioners or from pharmacies only
LM	Licensed merchant	For supply by a merchant licensed to sell animal remedies
CAM	Companion animal medicine	For supply by a retailer registered to sell such medicines

The selection of the route of supply of an animal remedy nationally is carried out by the HPRA in accordance with pre-defined legal criteria and, where relevant, agency policy. When the HPRA grants a marketing authorisation for an animal remedy it is obliged to allocate an appropriate category of supply in accordance with Schedule 1 of SI No. 786 of 2007. In deciding on the appropriate route at the time of the initial granting of the authorisation of an animal remedy, the agency must follow the designated criteria set out in the national legislation, as well as the benefit/risk balance of using the medicine concerned. The net effect is that antibiotics, controlled drugs, steroids and other potent drugs can only be available under prescription control or under the responsibility of a veterinary practitioner, while for other drugs, the HPRA has more freedom to decide on an appropriate supply route, on the basis of the risks involved. In order to give some benchmarks to the animal health industry regarding its perspective on the applicable criteria, the HPRA has developed national policies on:

- Methods of supply of veterinary vaccines
- Methods of supply of Companion Animal Antiparasitic Medicines
- Methods of supply of Companion Animal Antiparasitic Medicines (Addendum Report)

to help clarify the drivers and criteria for how veterinary medicines are allocated a supply category in this country. These policies are available on the HPRA website (www.hpra.ie).

In accordance with EU legislation, new medicines containing an active substance that has been authorised for fewer than five years must be restricted to prescription control (or veterinary practitioner use only).

The method allocated is subject to review and change based on the experience of the product on the market and on any change in the benefit/risk profile since the previous decision. The criteria for exempting certain veterinary medicinal products for food-producing animals from the requirement of

¹¹⁵ The European Communities (Animal Remedies)(No. 2) Regulations 2007 [SI No 786/2007].

a veterinary prescription were established in 2006 in the EU. These criteria require that only veterinary medicinal products that meet all of the following criteria can be exempted from the prescription requirements:

- (a) No particular knowledge or skill is needed in using the products,
- (b) The product does not present a risk, even if administered incorrectly,
- (c) There are not any warnings required in the product literature regarding potential serious side effects deriving from its correct use,
- (d) The product has not been the subject of frequent serious adverse reaction reporting,
- (e) No contraindications with other commonly used medicines are needed,
- (f) No special storage conditions are needed,
- (g) There is no risk to consumers even if the products are used incorrectly,
- (h) There is no risk of development of antimicrobial resistance or antiparasitic resistance even where the product is used incorrectly,

With the adoption of the new veterinary regulation in the European Parliament in December 2018, it is expected that a further review of the appropriateness of existing supply categories may be necessary ahead of the regulation coming into effect in January 2022.

Other regulatory controls affecting veterinary medicinal products

The importation of veterinary medicines into Ireland is regulated by DAFM. Prescribed medicines ('POMs') are dispensed in accordance with, and on presentation of, a veterinary prescription; therefore national legislation does not permit their supply via the internet or by mail order (HPRA understands that this includes having medicines supplied from overseas on foot of an Irish veterinary prescription that has been faxed abroad).

Veterinary medicines categorised as 'Licensed Merchant' (LM) may be sold without a veterinary prescription by outlets which are licensed by DAFM. Medicines authorised by the HPRA for animals that have a designated route of supply of 'LM' (Licensed Merchant) or 'CAM' (Companion Animal Medicine) may be purchased from internet sites or by mail order but only where the supplier is specifically licensed by DAFM. It is the responsibility of the user to ensure that veterinary medicines are sourced in accordance with the legislation.

In respect of veterinary medicines authorised centrally in the European Union, these may be supplied throughout the Community. In this case, the European Commission establishes the appropriate method of supply. In both situations, the allocation of an appropriate category of supply is based on an evaluation of the risks involved and taking account of the available legal categories which are defined by national and European legislation. As with medicines authorised nationally, the method of supply for products licensed centrally is also subject to review based on the experience with the product in the market and on any change in the benefit:risk profile.

Appendix 4: Members of the Task Force on Method of Supply of antiparasitic veterinary medicinal products that are indicated for food-producing animals

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