HPRA Annual Pharmacovigilance report for 2022

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ABBREVIATIONS

HPRA	Health Products Regulatory Authority
VMP	Veterinary medicinal product
SAR	Suspected adverse reaction
LEE	Lack of expected efficacy
SAE	Suspected adverse event
MAH	Marketing authorisation holder
VPA	Veterinary product authorisation
EMA	European Medicines Agency
NVR	New Veterinary Regulation

1. Introduction

The Health Products Regulatory Authority (HPRA) is an independent public sector organisation responsible for the regulation of health products, including veterinary medicinal products (VMPs). Part of our remit is the ongoing monitoring of the quality, safety and efficacy of authorised VMPs - a process known as 'pharmacovigilance'. This includes products that have been authorised nationally by the HPRA or centrally following the opinion of the European Medicines Agency. In relation to safety and efficacy, this role is fulfilled through a nationwide reporting system for adverse events (pharmacovigilance

system), which is designed to monitor products under actual use conditions. Veterinary pharmacovigilance underwent a significant change at the beginning of 2022 with the introduction of Regulation (EU) 2019/6, known hereafter as the new veterinary regulation (NVR). This regulation brought about substantial changes in how veterinary medicinal products are authorised, monitored and controlled in the European Union.

The scope of veterinary pharmacovigilance involves the surveillance of:

- Suspected adverse reactions (SAR) in animals to VMPs used under authorised conditions.
- Off-label use of VMPs in animals (i.e., where a product is not used according to its authorised summary of product characteristics (SPC)).
- Lack of expected efficacy (LEE) of VMPs.
- Reported violations of approved residue limits.
- Adverse reactions in humans related to the use of VMPs.
- Potential environmental problems.

These reports are collectively known as suspected adverse events (SAEs). Marketing authorisation holders (MAHs) are pharmaceutical companies that have been granted approval to market a VMP. MAHs are required to report all SAEs occurring in Ireland to a central Union Pharmacovigilance database (UPhD) within 30 days. Reports may also be submitted directly to the HPRA by veterinary healthcare professionals and animal owners. SAE reports received by the HPRA are collated and evaluated by the HPRA and relevant MAHs. In the event that a safety issue is identified through this surveillance, appropriate steps can be taken to reduce the level of any associated risk, for example, by updating the Summary of Product Characteristics (SPC) and/or associated labelling and package leaflet.

SPC: A document providing officially approved information on a VMP

The minimum requirements for an SAE report to be considered valid are detailed in Table 1.

Table 1: Suspected Adverse Events - minimum information required

An SAE report will be considered valid when at least the following core information is provided:
▪ **an identifiable reporter (e.g., veterinary surgeon/veterinary nurse, pharmacist, animal owner)**
▪ **animal/human details: species, age, sex**

- **the name and veterinary product authorisation (VPA) number of the product in question**
- **details of the adverse event**

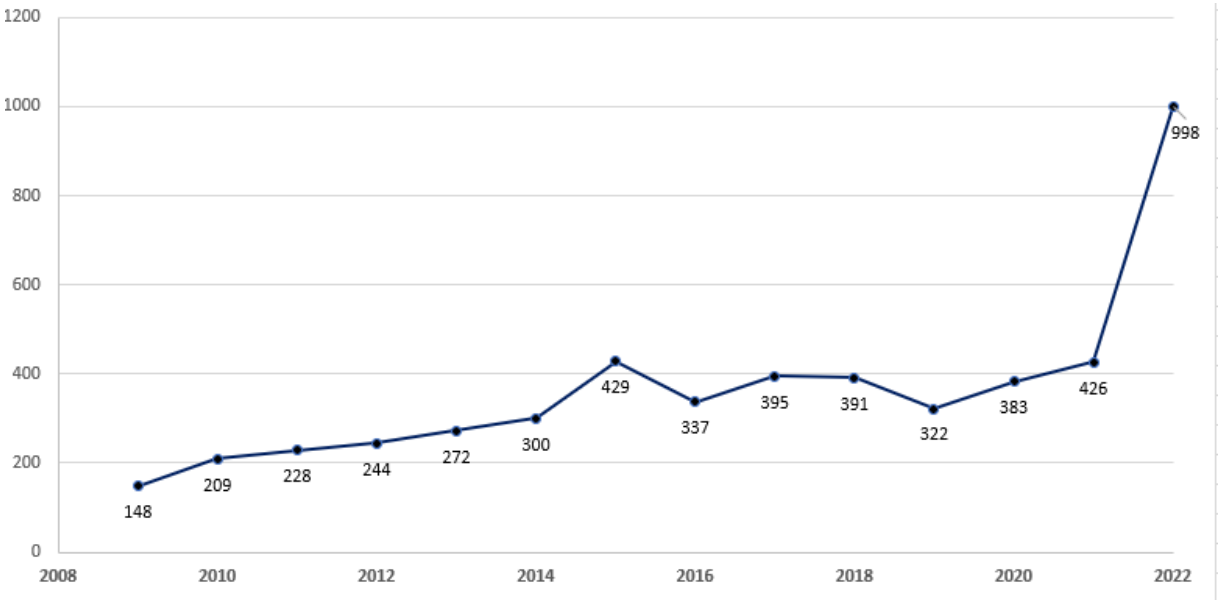
While the above outlines the minimum requirements for a valid SAE report, the reporter should endeavour to provide as comprehensive an account as possible in order to facilitate a full scientific evaluation. Where relevant, this may include the provision of laboratory test results and necropsy findings.

2. National Pharmacovigilance Surveillance

Over the course of 2022, 29 reports of suspected adverse events to veterinary medicines were reported directly to the HPRA, from veterinarians and animals owners.

However, a total of 998 adverse event reports occurring in Ireland were recorded in the UPhD over the course of 2022. Prior to the introduction of the NVR, only reports classified as serious were recorded in the UPhD. However, as of 28th January 2022, all reports, including serious and non-serious must be recorded. Given these changes in reporting requirements, the total number of adverse event reports for 2022 is significantly higher and therefore not directly comparable to previous years (see Figure 1).

Figure 1: Total number of SAE Reports to the HPRA from 2009-2022



As detailed in Figure 2 below, there were a large number of adverse event reports recorded in the UPhD in the month of February, being the first month following the introduction of the new system and possibly including historical reports.

Figure 2. Overview of reports recorded per month in 2022

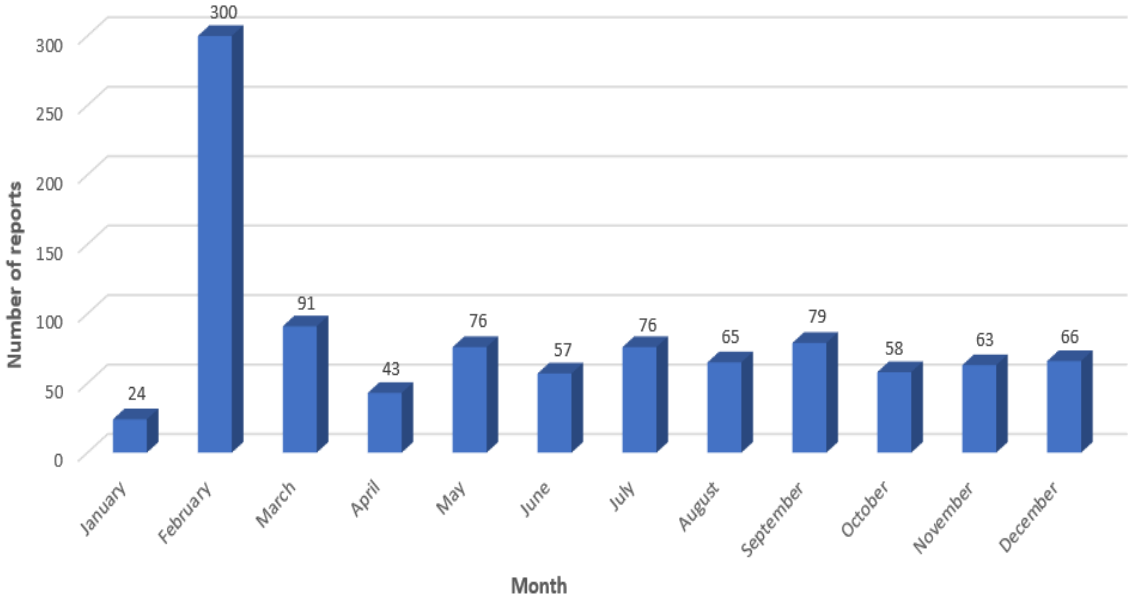
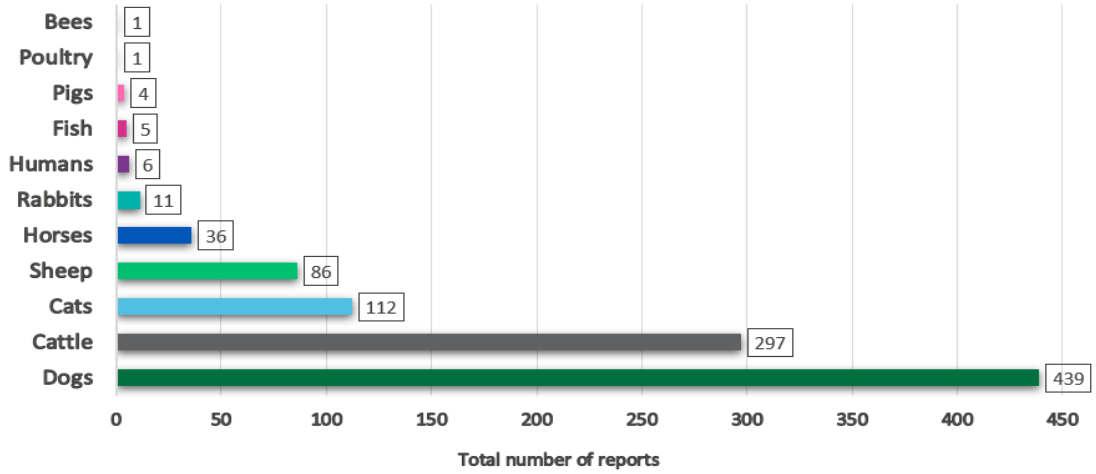


Table 2. Overview of reports recorded in 2022

Species	Total number reports	Total number of animals reacting
Food producing animals		
Cattle	297	10,345
Sheep	86	3,104
Horses	36	87
Pigs	4	254
Fish	5	64,000
Bee	1	unknown
Poultry	1	50
Companion animals		
Dogs	439	2,038
Cats	112	139
Rabbits	11	11
Other		
Human	6	6
Total	**998**	**80,035**

Figure 3: Number of SAE reports per species in 2022



As illustrated in the above graph (Figure 3), the highest number of adverse event reports occurred in dogs (439 reports involving 2,039 reacting animals). The second highest number of adverse event reports occurred in cattle (297 reports involving 10,345 reacting animals). This follows a similar trend to previous years in terms of the most affected target species (in 2021, 181 reports involving 343 reacting animals were recorded for dogs and 137 reports involving 2,497 reacting animals were recorded for cattle). However, in 2022, the third highest number of adverse events reports occurred in cats (112 reports involving 139 reacting animals) whereas in 2021, the third highest number of adverse event reports were recorded in sheep (50 reports involving 1,014 reacting animals).

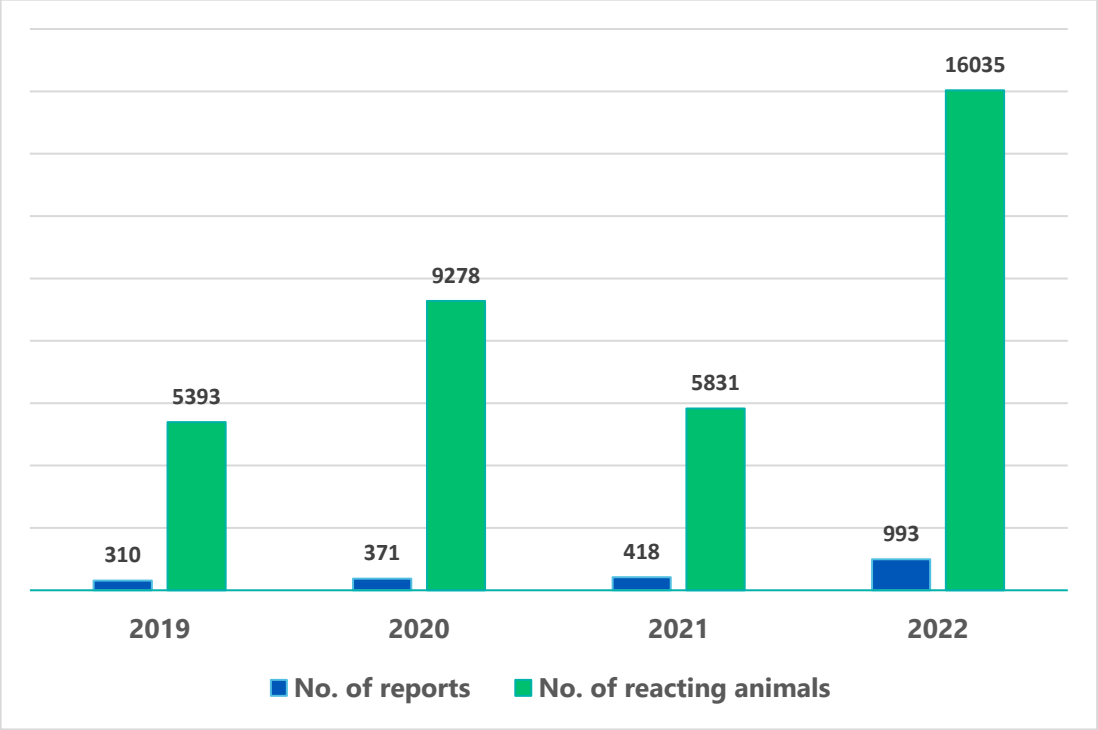
As in previous years, fish was the species for which the highest number of affected animals were reported (64,000 animals). However, this represents a reduction in the number of affected animals compared to the previous year when a total of 377,000 reacting animals was recorded.

A direct comparison of the number of reports and consequently, the number of reacting animals recorded in 2022 with previous years is not possible due to the changed approach to reporting adverse events to the UPhD. However, the following table and chart summarises the number of reports and the number of reacting animals with the species fish excluded given that the number of fish involved in individual reports is substantially higher compared to all other target species and therefore skews the figures.

Table 3. Overview of number of reports and reacting animals from 2019 to 2022

Year	2019	2020	2021	2022
Number of reports	310	371	418	993
Total number of reacting animals	5,393	9,278	5,831	16,035

Figure 4: Number of SAE reports and reacting animals (excluding fish) in 2022



Until the data for 2023 is available, it is not possible to determine whether the increased number of reports and reacting animals represents a true increase or is fully accounted for by the inclusion of non-serious adverse events that had not been submitted previously.

In relation to reports in dogs for 2022, the medically important VeDDRA terms (clinical signs) most frequently reported following use of all veterinary medicinal products are listed in Table 4 below. A medically important VeDDRA term is defined as '*serious medical concepts often causally associated with drugs across multiple pharmacological/therapeutic classes*'. It is important to note that multiple VeDDRA terms can be included in the same report, so the total below does not equate to the total number of reports.

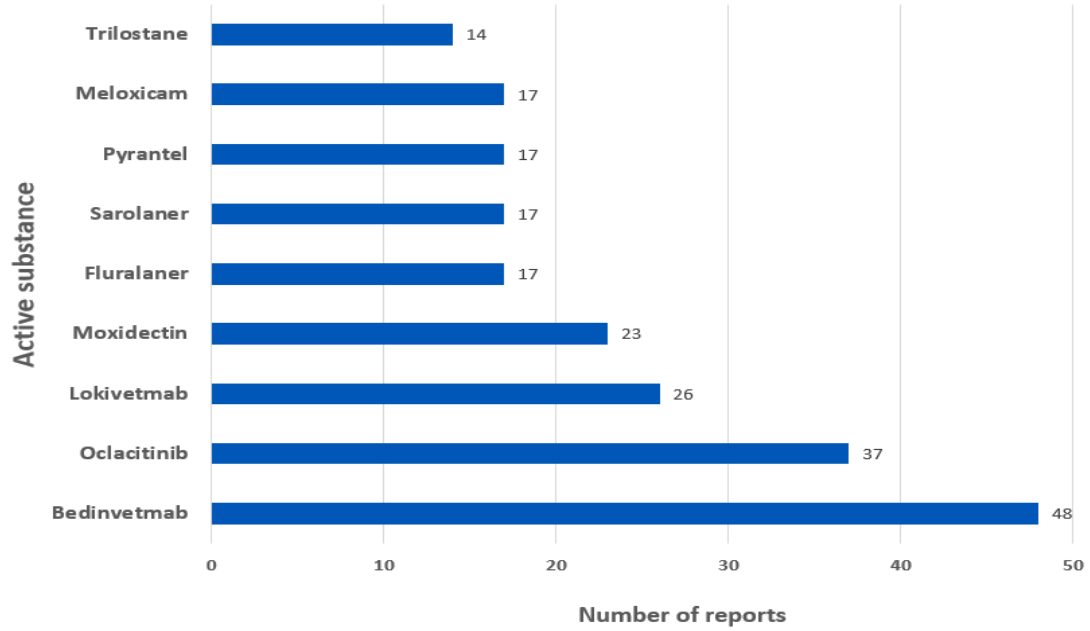
Table 4. Most frequently reported medically important VeDDRA terms for dogs in 2022

Medically important VeDDRA term	Number of reports	Number of animals affected
Death	26	29
Seizure	14	14
Hypersensitivity reaction	12	12
Anaphylaxis (severe allergic reaction)	6	6
Aggression	5	5
Deafness/Loss of hearing	5	5

Diabetes mellitus	5	5
Thrombocytopenia (low platelet count)	4	4
Abdominal pain	3	3
Blindness	3	3
Paresis (muscle weakness)	3	3
Circulatory shock	2	2

Figure 5 below illustrates the most frequently reported active substances following use of pharmaceutical veterinary medicinal products in dogs, excluding reports of lack of expected efficacy. It is important to note that multiple active substances can be included in the same report, so the total below does not equate to the total number of reports.

Figure 5: Most frequently reported active substances concerning reports in dogs in 2022



It should be noted that the three active substances with the highest number of reports of adverse events in 2022 relate to newer classes of compounds (monoclonal antibodies, janus kinase inhibitors) which are comparatively new to the market and like all newer products, their novelty can result in an initial period of increased reporting of adverse events.

The species with the second highest number of adverse event reports occurring in Ireland in 2022 was cattle (297 reports). The medically important VeDDRA terms reported most frequently in cattle following use of all veterinary medicinal products are listed in Table 5 below.

Table 5. Most frequently reported medically important VeDDRA terms for cattle in 2022

Medically important VeDDRA term	Number of reports	Number of animals affected
Death	50	140
Recumbency (lying down)	4	24
Anaphylaxis (severe allergic reaction)	2	20
Blindness	2	8
Collapse	2	18
Anorexia	1	1
Paresis (muscle weakness)	1	5
Acute Mastitis	1	18
Abdominal pian	1	50
Renal (kidney) disorder	1	7

Figure 6 below illustrates the most frequently reported active substances following use of pharmaceutical veterinary medicinal products in cattle, excluding reports of lack of expected efficacy. It is important to note that multiple active substances can be included in the same report, so the total below does not equate to the total number of reports.

Figure 6: Most frequently reported active substances in cattle in 2022

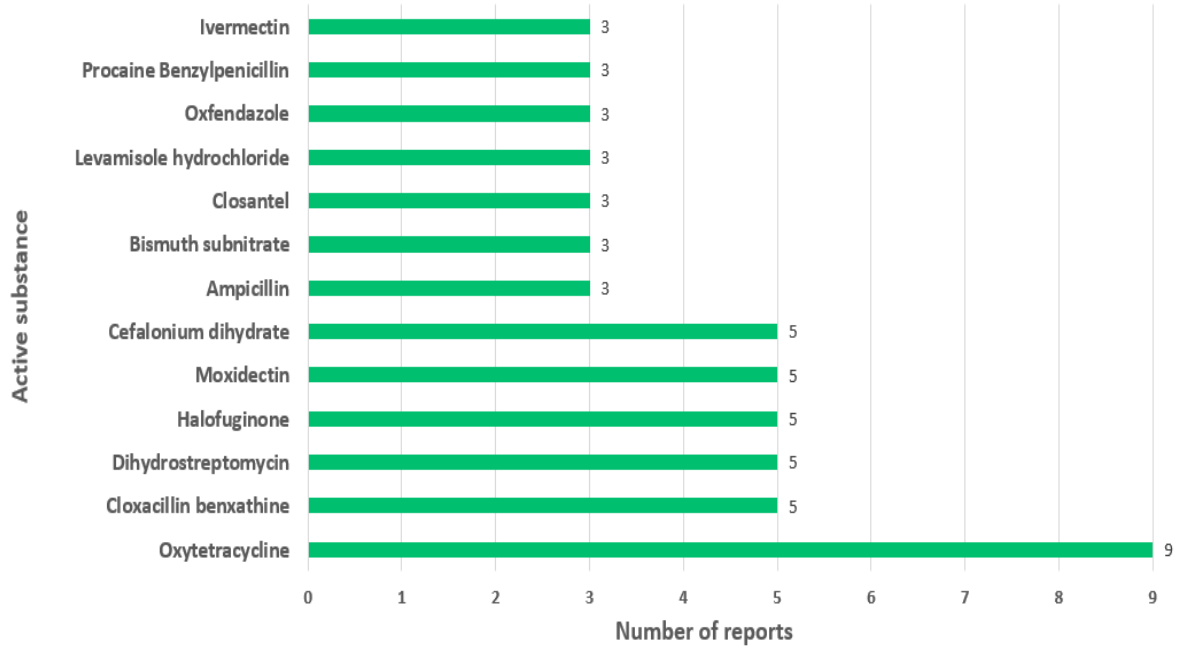
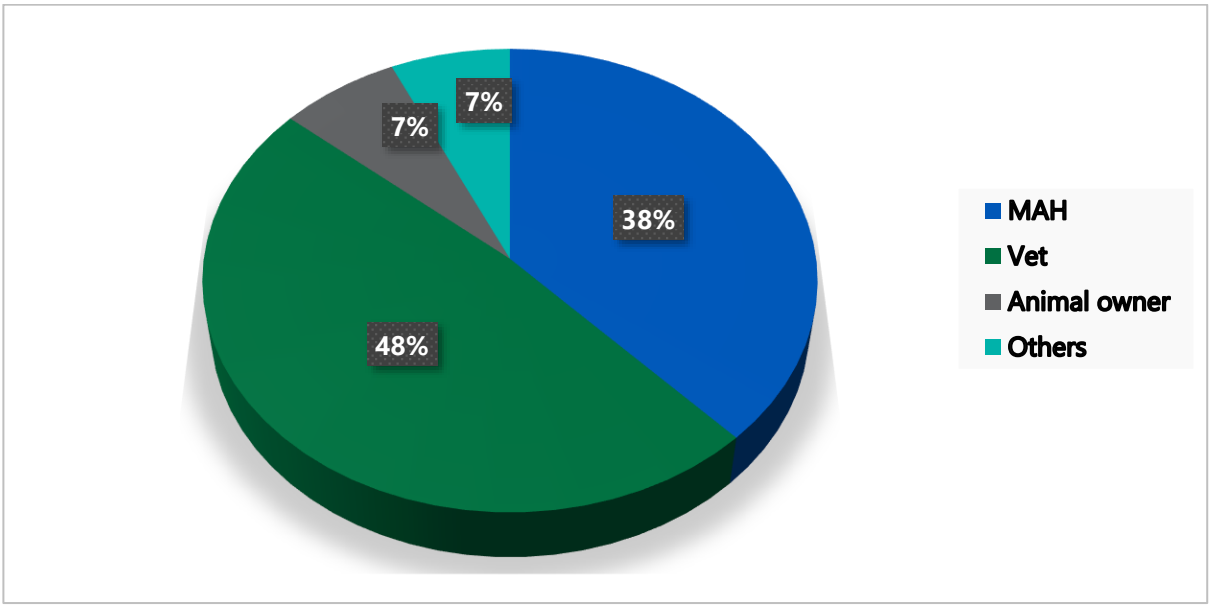


Figure 7: Number of SAE reports by reporting source in 2022



As illustrated in Figure 7 above, of the 29 adverse event reports submitted directly to the HPRA in 2022, 14 reports were submitted by veterinarians representing approximately 48% of all reports. Eleven reports were submitted by MAHs (representing approximately 38% of all reports), two reports were submitted by animal owners (representing approximately 7% of all reports) and two reports were submitted from other sources.

As MAHs no longer submit adverse event reports directly to the HPRA, the percentage of adverse event reports submitted by veterinarians has risen compared to previous years as illustrated in Table 6 below.

Table 6. Adverse event reports submitted by veterinarians in 2022

Year	2019	2020	2021	2022
Number of reports submitted by veterinarians	19	12	9	14
Percentage of reports submitted by veterinarians	5.9%	3.1%	2.1%	48%

As in previous years, the total number of reports submitted to the HPRA by veterinarians remains low. It is likely that the majority of reports reported to MAHs originate from veterinarians and veterinary healthcare professionals. In order to raise awareness of veterinary pharmacovigilance in general and importantly, to encourage the reporting of adverse events by veterinarians and veterinary healthcare professionals, the HPRA published a series of video presentations in 2022 including one prepared specifically for vets, vet nurses and animal healthcare professionals to explain the importance and encourage the reporting of adverse events following use of veterinary medicines.

The video provides useful information on how safety and effectiveness of medicines is ensured, the different types of adverse events, the importance of reporting adverse events in addition to how and to

whom adverse events should be reported. This and other pharmacovigilance-related information is available on the HPRA website under 'Adverse event reporting'.

Of the 998 reports that were recorded during 2022, 576 involved suspected adverse reactions representing approximately 57.7% of all reports, 424 reports related to a lack of expected efficacy (LEE) representing approximately 42.5% of all reports, 17 reports related to potential residue violations representing approximately 1.7% of all reports and 6 reports involved human reactions representing approximately 0.6% of all reports (see Figure 8 below).

Twenty-five reports related to both adverse reactions and a lack of expected efficacy, so these reports have been counted twice and therefore the number of reports is higher than 998.

Figure 8: Number and type of adverse event reports received in 2022

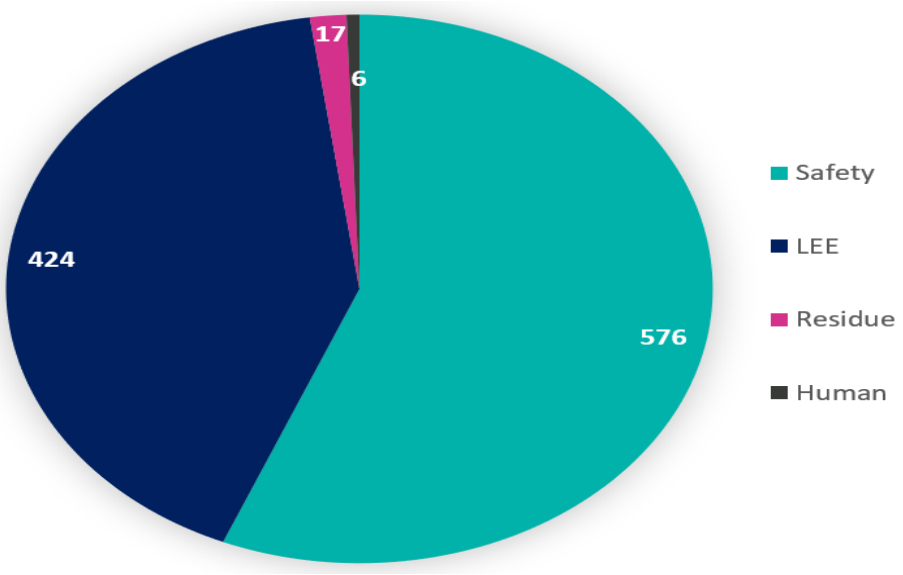
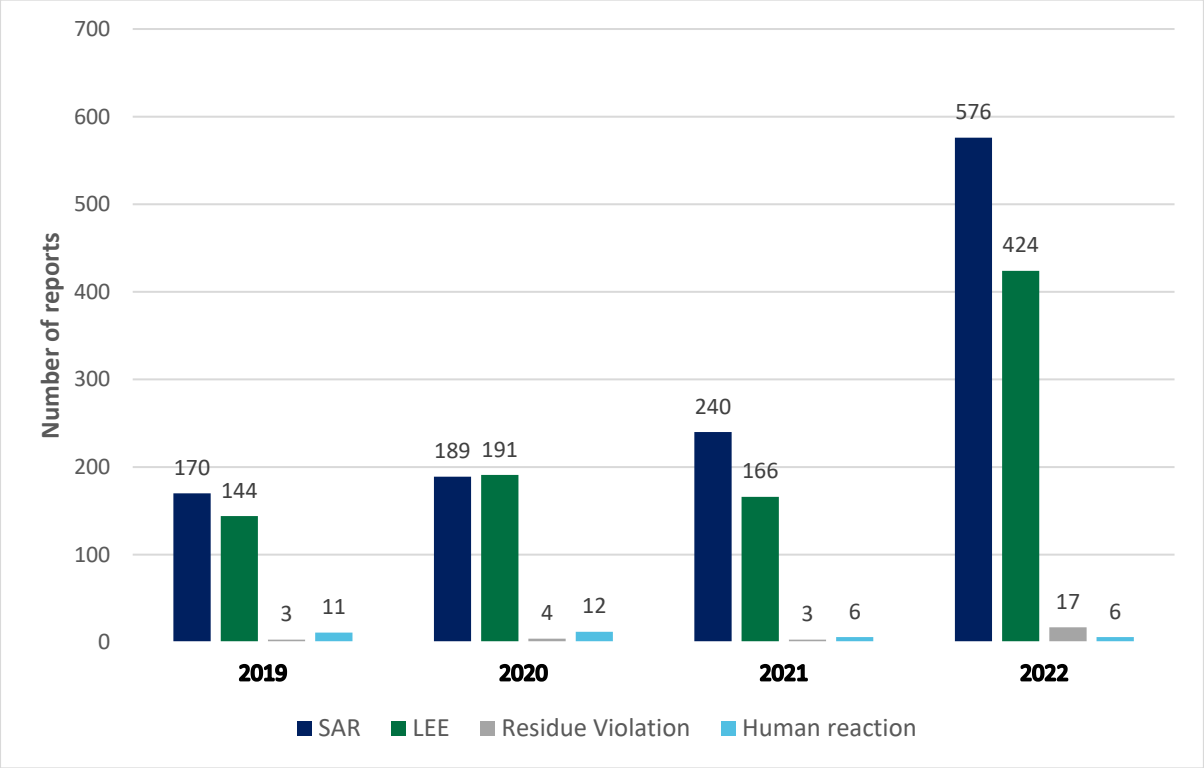


Figure 9 below illustrates a comparison of the number and types of reports received from 2019 to 2022.

Figure 9: Number of SAE reports by category received from 2019 to 2022



As noted above, 576 reports were in relation to suspected adverse reactions (SAR) only. Table 7 below summarises the number of reported products (both pharmaceutical/immunological) grouped according to their intended route of administration for cattle, dogs and humans.

In 2022, for cattle, dogs and humans the most frequently reported product type involved in adverse reactions was injectable products followed by products for oral administration. It is important to note that multiple product types can be included in the same report, so the total below does not equate to the total number of reports.

Table 7. Number of suspected adverse reactions by product type for cattle, dogs and humans in 2022.

Type of product	Species		
	Cattle	Dogs	Humans
Injectable	33	244	4
Oral	10	101	0
Intramammary	13	0	0
Topical	4	18	2
Other	1	2	0
Total	**61**	**365**	**6**

2.1. Adverse reactions following human exposure

Six reports of human exposure to VMPs were received during 2022. Four of these reports were received following exposure to immunological products and two reports arose from exposure to a pharmaceutical product. The most common clinical symptoms reported included injection site swelling and injection site pain.

Those administering VMPs are reminded to exercise due caution when handling veterinary medicinal products and to pay particular attention to any special precautions for the use of individual products as detailed in the relevant product information (SPC) published on the HPRA website or on the package labelling/leaflet accompanying the product.

2.2 Reports of lack of expected efficacy

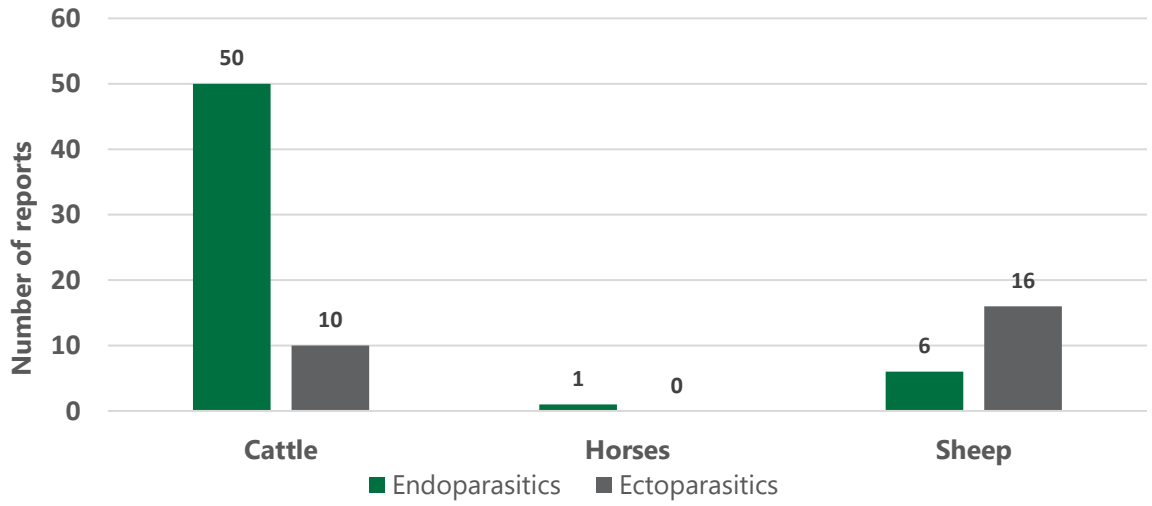
There were 318 reports relating solely to lack of expected efficacy (LEE) reported in 2022.

Of these reports, 175 relate to cattle, 54 relate to dogs, 45 relate to sheep, 20 relate to horses, 10 relate to cats, 5 relate to fish, 4 relate to pigs, 4 relate to rabbits and one report relates to bees.

Where it is not specified within an adverse event report if the product in question was administered according to its authorised SPC, a worst-case scenario is assumed i.e., the product will be considered to have been used as recommended.

Of the 318 reports of suspected LEE, some 60 reports in cattle, 32 reports in sheep and one report in horses were identified by MAHs as LEE following administration of an antiparasitic (either endoparasitic or ectoparasitic) veterinary medicinal product (Figure 10).

Figure 10: Reports of suspected lack of efficacy following use of antiparasitic products in cattle, sheep and horses in 2022



However, it should be noted that these LEE reports only represent a subcategory of LEE reports following use of antiparasitic veterinary medicinal products and therefore the above values are likely to be under-representative of the true number of reports associated with suspected lack of expected efficacy following administration of antiparasitic veterinary medicinal products.

3. European Pharmacovigilance Issues

3.1 Changes to Pharmacovigilance arising from the new veterinary Regulation (EU) 2019/6

Significant changes to veterinary pharmacovigilance were introduced following the introduction of the NVR on 28 January 2022. These include the management of signals from the centralised database of SAEs in the European Union, as well as process changes in relation to how responsibility for their review is shared between MAHs and Member States.

3.2 Signal Management

One of the most significant changes arising from the introduction of the NVR was the introduction of a formal responsibility for 'signal management'.

> **'Signal'** means information that arises from one or multiple sources, which suggests a potentially new causal association, or a new aspect of a known causal association between an intervention and an adverse event or a set of related adverse events, that is judged likely to justify further investigation of possible causality.

Although signal detection had previously formed part of the post-marketing safety monitoring of veterinary medicines, the introduction of the NVR gave for the first time, a formal legal basis for such pharmacovigilance activities .

The NVR requires MAHs to carry out a signal management process for all of their VMPs. The signal management process enables continuous monitoring of all SAEs associated with a product, any potential impact such reports may have on the benefit-risk balance of a VMP and forms a core element of the pharmacovigilance system. MAHs must record at least annually all results and outcomes of the signal management process in the UPhD. A Signal Management Expert Group (SMEG) was established by the European Medicines Agency in collaborations with national competent authorities with the goal of co-ordinating the signal management process across the EU.

The HPRA has taken a lead role in performing a significant amount of signal detection work within the

SMEG on behalf of the European regulatory network, using a risk-based and a data-driven approach.

The outcome of signal management can result in either the signal being refuted (no further action is required), the signal requires close monitoring (MAHs should continue to monitor the signal with a view to potentially updating the product information if necessary) or the signal results in a proposal for regulatory action (e.g., an update to the product information). If the MAH proposes an update to the product information based on the outcome of their signal management processes, this is implemented by way of a variation application (variation requiring assessment) submitted to all Member States where the product is authorised.

4. Achievements

During 2022, the HPRA pharmacovigilance team delivered on a number of key initiatives, which included:

- Implemented a number of new internal work processes to accomodate the changes in regulatory requirements arising from the NVR.
- Reviewed all adverse event reports originating in Ireland that have been recorded in the UPhD.
- Published a number of updates on the implementation of the NVR and the changes in requirements for veterinary pharmacovigilance (these updates are available on the HPRA website).
- A Veterinary Information day was held in May 2022 at which a presentation was made outlining the changes in requirements for veterinary pharmacovigilance (a recording of the presentations along with a Questions and Answers are available on the HPRA website.
- Processed 20 variation applications in order to update the product information as a result of post-marketing pharmacovigilance data i.e., to include new or revised warnings to more accurately reflect the adverse events that have been experienced following field use of the concerned product.
- Processed 19 variation applications in order to update the reference number and location of the PSMF in the Union Product database.
- Processed 30 variations to update the information for the qualified person responsible for pharmacovigilance (QPPV) in the UPhD.
- Conducted 2 pharmacovigilance inspections aimed at ensuring compliance with regulatory requirements.
- Published three voiced-over video presentations detailing adverse event reporting and general information for animal owners, vets and veterinary nurses and other animal healthcare professional (these are available under the Adverse Reaction/Event Reporting tab on the veterinary section of the HPRA website).

5. Conclusion

Veterinary professionals as well as persons licensed to sell or supply animal remedies are reminded of their obligation to notify the HPRA or the relevant MAH of all suspected adverse events, in particular, serious adverse events, all unexpected adverse reactions and all symptomatic human adverse events associated with the use of VMPs should be reported.

The HPRA recognises that there may be a perception amongst the veterinary profession that contacting the HPRA will adversely impact on their workload, in that they may be asked to engage in discussion of the adverse event or case history; however, this is rarely the case. The reporting process itself is simple; reports may be submitted via a number of different methods and veterinary practitioners are encouraged to enlist their veterinary nurse colleagues' help in discharging their responsibilities to report adverse events. Provided that the mandatory information is included in the report, there will normally be no need for the HPRA to consult with the reporter. The HPRA will routinely acknowledge the report and use the information provided to contribute to the overall safety monitoring of the product in question.

Adverse events can be reported using an online reporting form accessed via the homepage of the HPRA website. Alternatively, adverse event report forms may be downloaded from the HPRA website for off-line completion and can be sent by freepost to the HPRA, or prepaid self-addressed forms can be requested from the Veterinary Sciences Department of the HPRA.

Further information on the topic of veterinary pharmacovigilance can be obtained from the Safety Information section of the HPRA website.

Each of the Annual Pharmacovigilance reports from 2014 to present, are published on the HPRA website and are available here.

Useful references and links

European Medicines Agency (2021), *Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Collection and recording of suspected adverse events for veterinary medicinal products.* Available at: https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-collection-recording-suspected_en.pdf

European Medicines Agency (2021), *Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Signal Management.* Available at: https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-signal-management_en.pdf

European Medicines Agency Pharmacovigilance-related recommendations to product information for centrally authorised veterinary medicines. Available at: https://www.ema.europa.eu/en/veterinary-

regulatory/post-authorisation/pharmacovigilance/pharmacovigilance-related-recommendations-product-information-centrally-authorised-veterinary

European Medicines Agency Annual bulletins on veterinary pharmacovigilance activities (2003-2019). Available at: Annual bulletins on veterinary pharmacovigilance activities (2003-19) | European Medicines Agency (europa.eu)

European Medicines Agency (2022), *Veterinary Medicinal Products Regulation*. Available at: https://www.ema.europa.eu/en/veterinary-regulatory/overview/veterinary-medicinal-products-regulation

Health Products Regulatory Authority (2021), *Report an Issue,* Available at: https://www.hpra.ie/homepage/about-us/report-an-issue

Health Products Regulatory Authority (2021), *Developments on the implementation of Regulation 2019/6 - Monthly updates*. Available at: https://www.hpra.ie/homepage/veterinary/regulatory-information/implementation-of-the-new-veterinary-regulation-(regulation-2019-6)/monthly-update

Health Products Regulatory Authority (2022), *Pharmacovigilance - Pharmacovigilance legislation*. Available at: http://www.hpra.ie/homepage/veterinary/regulatory-information/medicines-authorisation/pharmacovigilance-guidance-documentation.