HPRA Annual Pharmacovigilance report for 2023

Michelle Mulchrone BSc. RVN
Alma Moffett BSc.VN, BA
Aisling Kavanagh BSc. RVN PgDip
Megan McDowall RVN
Paul McNeill MVB, MSc. DLSHTM, MRCVS

Veterinary Sciences Department,
Health Products Regulatory Authority,
Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2

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
UPhD	Union Pharmacovigilance Database

1. Introduction

The Health Products Regulatory Authority (HPRA) is 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) under actual use conditions. The new veterinary Regulation (NVR) introduced in 2022 brought about substantial changes in how VMPs 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 2023, a total of 835 suspected adverse event reports occurring in Ireland were recorded in the UPhD of which 15 were reported directly to the HPRA from veterinarians and animal owners.

Following the introduction of the NVR in January 2022, all reports, including serious and non-serious must be recorded in the UPhD. As a result of this requirement to report non-serious reports, the number of adverse events reported increased significantly in 2022 (998 reports) compared to previous years. The number of reports has reduced slightly in 2023 (835 reports) compared to 2022, and this is believed to be as a result of recording historical reports in 2022. (See figure 1)

Figure 1: Total number of SAE Reports to the HPRA (2009-2021) and to the Union Pharmacovigilance Database (UPhD) (2022-2023)

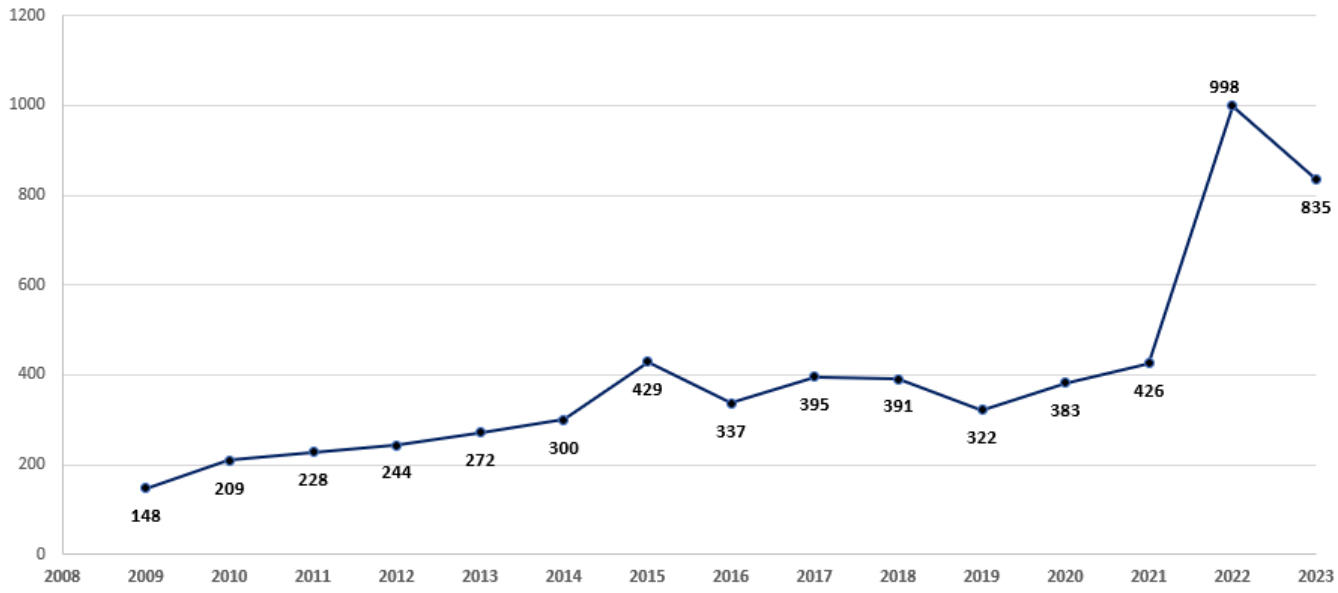


Figure 2. Monthly overview of reports of adverse events occurring in Ireland in 2023

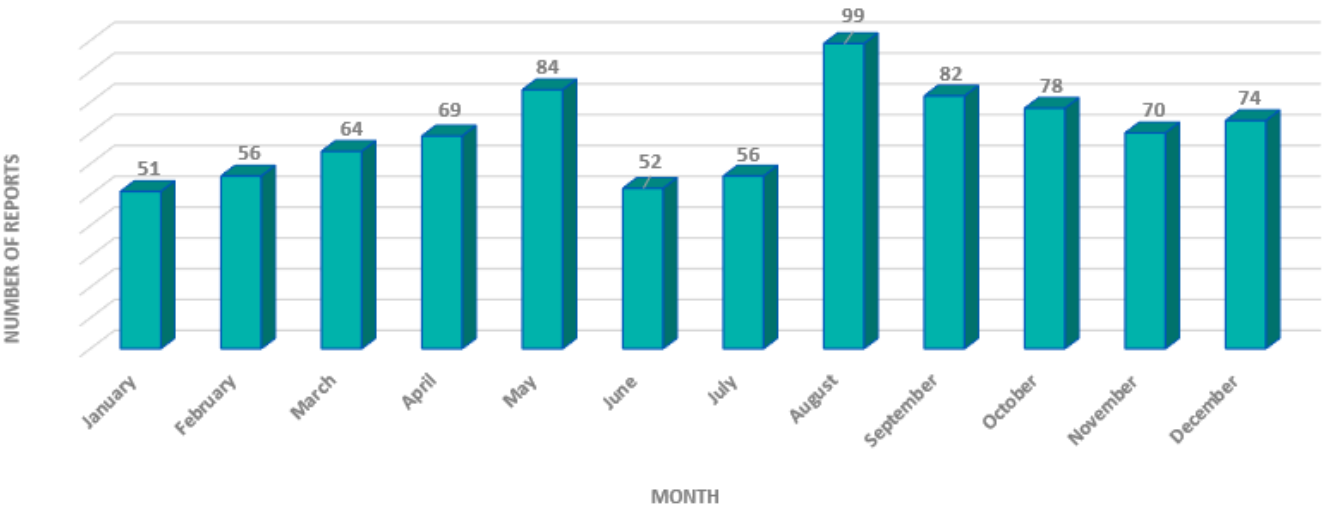
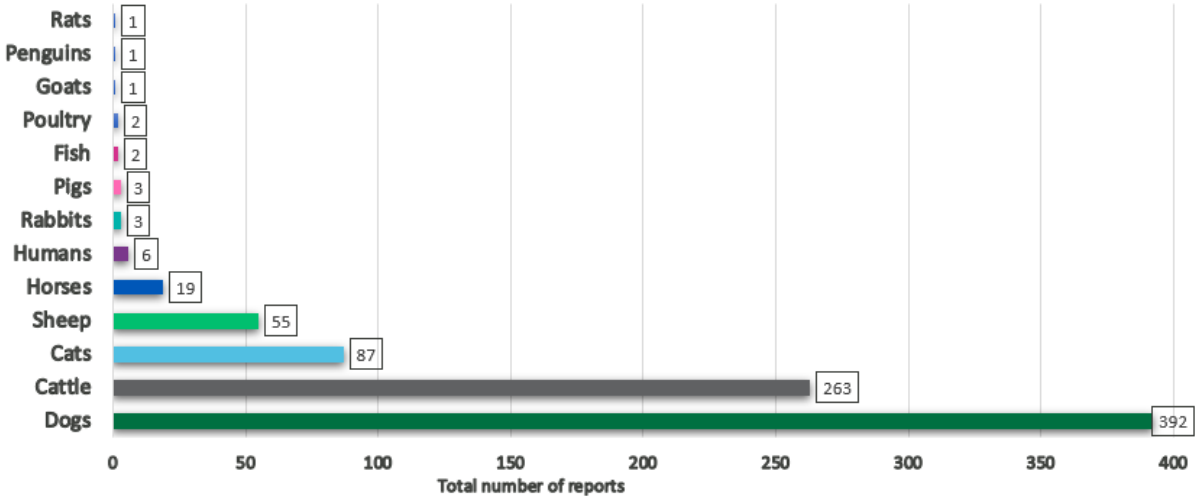


Table 2. Breakdown of reports recorded in 2023

Species	Total number reports	Total number of animals reacting
Food producing animals		
Cattle	263	7,463
Sheep	55	1,274
Horses	19	22
Pigs	3	562
Fish	2	30,000
Poultry	2	506
Goats	1	7
Companion animals		
Dogs	392	709
Cats	87	97
Rabbits	3	3
Rats	1	1
Other		
Penguins	1	1
Other		
Humans	6	6
Total	**835**	**40,651**

Figure 3: Number of SAE reports per species in 2023



As illustrated in the above graph (Figure 3), the highest number of adverse event reports occurred in dogs (392 reports involving 709 reacting animals). The second highest number of adverse event reports occurred in cattle (263 reports involving 7,463 reacting animals). This follows a similar trend to previous years in terms of the most affected target species (in 2022, 439 reports involving 2039 reacting animals were recorded for dogs and 297 reports involving 10,345 reacting animals were recorded for cattle). As in 2022, the third highest number of adverse event reports occurred in cats (87 reports involving 97 reacting animals)

As in previous years, fish was the species for which the highest number of affected animals were reported (30,000 animals). However, this represents a reduction in the number of affected animals compared to the previous year when a total of 64,000 reacting animals was recorded.

The following table summarises the number of reports and the number of reacting animals excluding the reports in fish, given that the number of fish involved in individual reports is substantially higher compared to all other target species and therefore skews the data.

Table 3. Overview of number of reports and reacting animals from 2019 to 2023

Year	**2019**	**2020**	**2021**	**2022**	**2023**
Number of reports	310	371	418	993	835
Total number of reacting animals	5,393	9,278	5,831	16,035	**10,651**

Note that the number of reports for 2019-2021 only includes serious adverse event reports reported directly to the HPRA whereas from 2022 onwards, all adverse event reports recorded in the UPhD database are included.

In relation to reports in dogs for 2023, the medically important VeDDRA terms (clinical signs) most frequently reported following use of all VMPs 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.

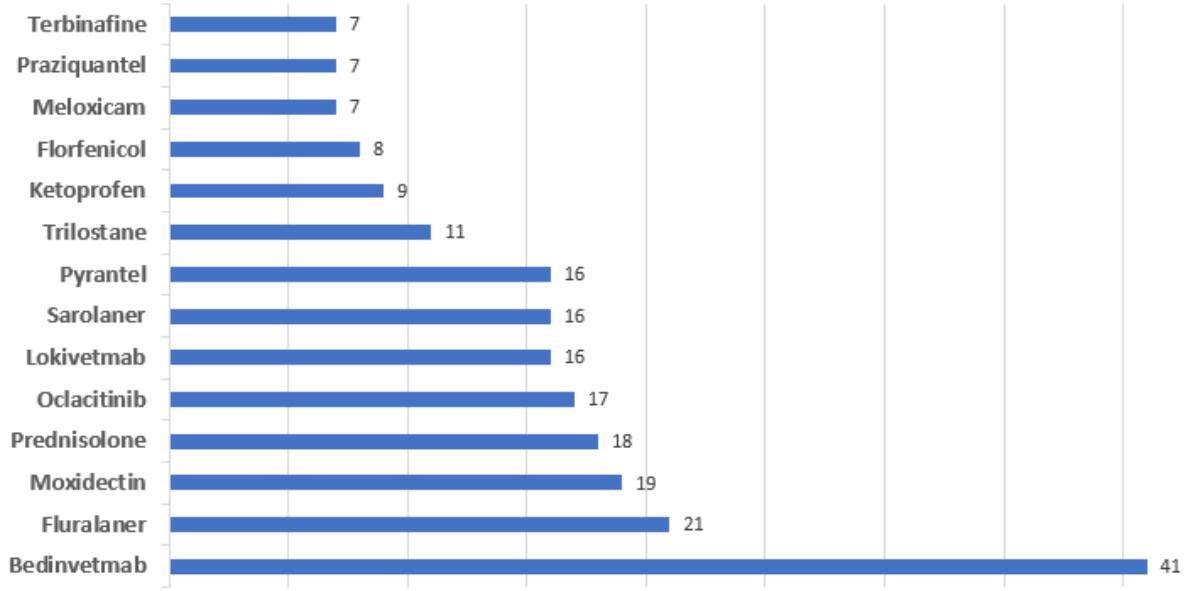
Table 4. Most frequently reported medically important VeDDRA terms for dogs in 2023

Medically important VeDDRA term	Number of reports	Number of animals affected
Death	28	34
Seizure	30	30
Hypersensitivity reaction	10	10
Anaphylaxis (severe allergic reaction)	6	6
Thrombocytopenia (low platelet count)	5	5
Aggression	4	4
Deafness/Loss of hearing	4	4
Abdominal pain	4	4
Blindness	2	2
Paresis (muscle weakness)	2	2

The four most frequently reported medically important VeDDRA terms (death, seizure, hypersensitivity reaction, anaphylaxis) for dogs in 2023 are the same as those reported for 2022.

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 2023



As in 2022, the active substance with the highest number of reports of adverse events in 2023 (bedinvetmab) concerns a product containing monoclonal antibodies which is comparatively new to the market and like all newer products, their novelty can result in an initial period of increased reporting of adverse events.
However, there were slightly fewer reports involving this active substance in 2023 (41) compared to 2022 (48).

The species with the second highest number of adverse event reports occurring in Ireland in 2023 was cattle (263 reports). The medically important VeDDRA terms reported most frequently in cattle following use of all VMPs are listed in Table 5 below.

Table 5. Most frequently reported medically important VeDDRA terms for cattle in 2023

Medically important VeDDRA term	Number of reports	Number of animals affected
Death	68	1416
Recumbency/Lying down	9	35
Anaphylaxis (severe allergic reaction)	7	8
Blindness	7	32
Collapse	3	3
Acute Mastitis	1	2

The four most frequently reported medically important VeDDRA terms (death, recumbency, anaphylaxis, blindness) for cattle in 2023 are the same as those reported for 2022.

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 2023

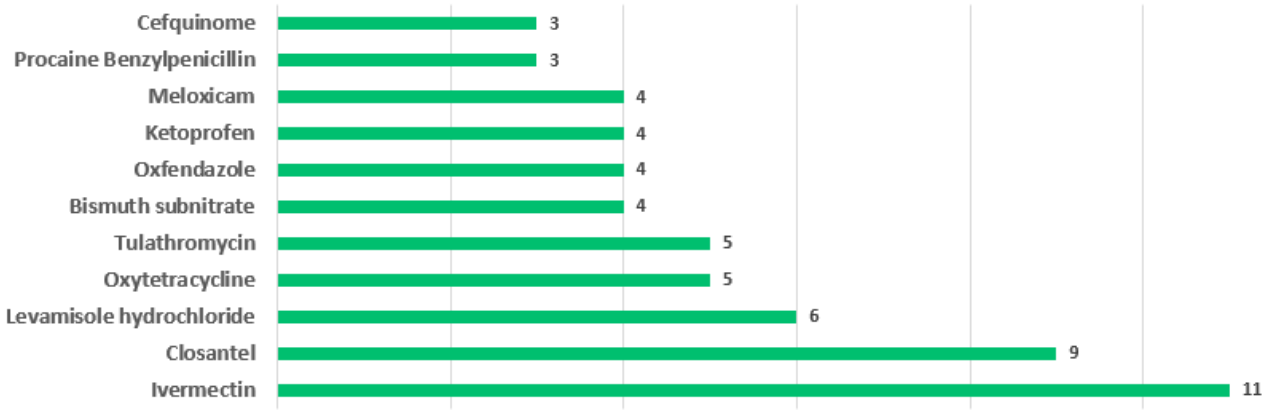
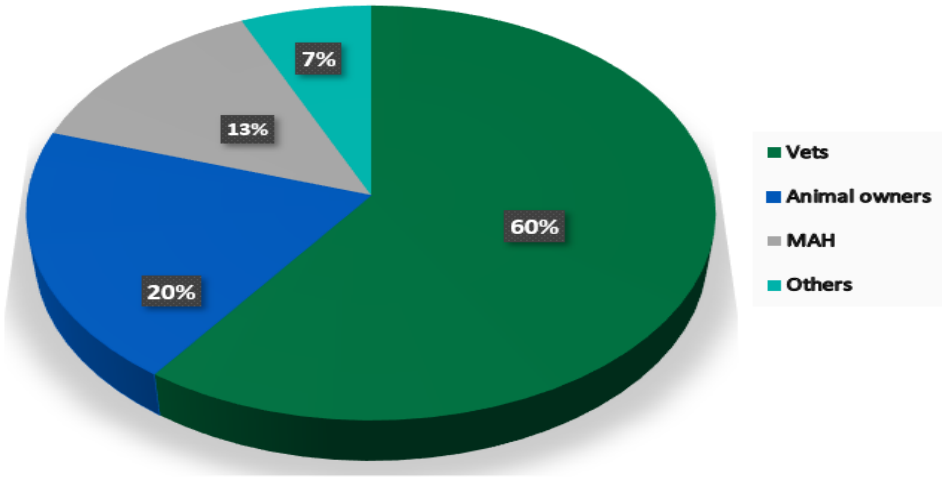


Figure 7: Number of SAE reports by reporting source in 2023



As illustrated in Figure 7 above, of the 15 adverse event reports submitted directly to the HPRA in 2023, 9 reports were submitted by veterinarians representing 60% of all reports. Three reports were submitted by animal owners (representing 20% of all reports), two reports were submitted by MAHs (representing approximately 13% of all reports) and one report was submitted from the DAFM (representing approximately 7% of all reports).

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 2023

Year	2020	2021	2022	2023
Number of reports submitted by veterinarians	12	9	14	9
Percentage of reports submitted by veterinarians	3.1%	2.1%	48%	60%

2.1 Number and type of adverse event reports

Of the 835 reports that were recorded during 2023, 488 involved suspected adverse reactions; 325 reports related to a lack of expected efficacy (LEE); 16 reports related to possible residue violations and 6 reports involved human reactions, representing approximately 58%, 39%, 2% and 1% respectively of all reports (see Figure 8 below).

Note that 88 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 835.

Figure 8: Number and type of adverse event reports received in 2023

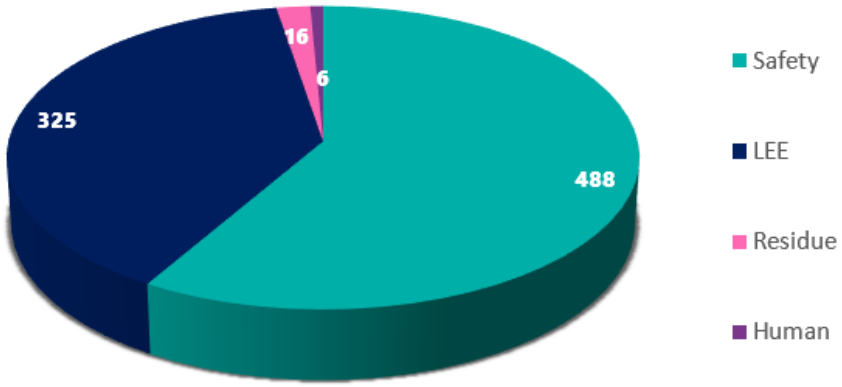
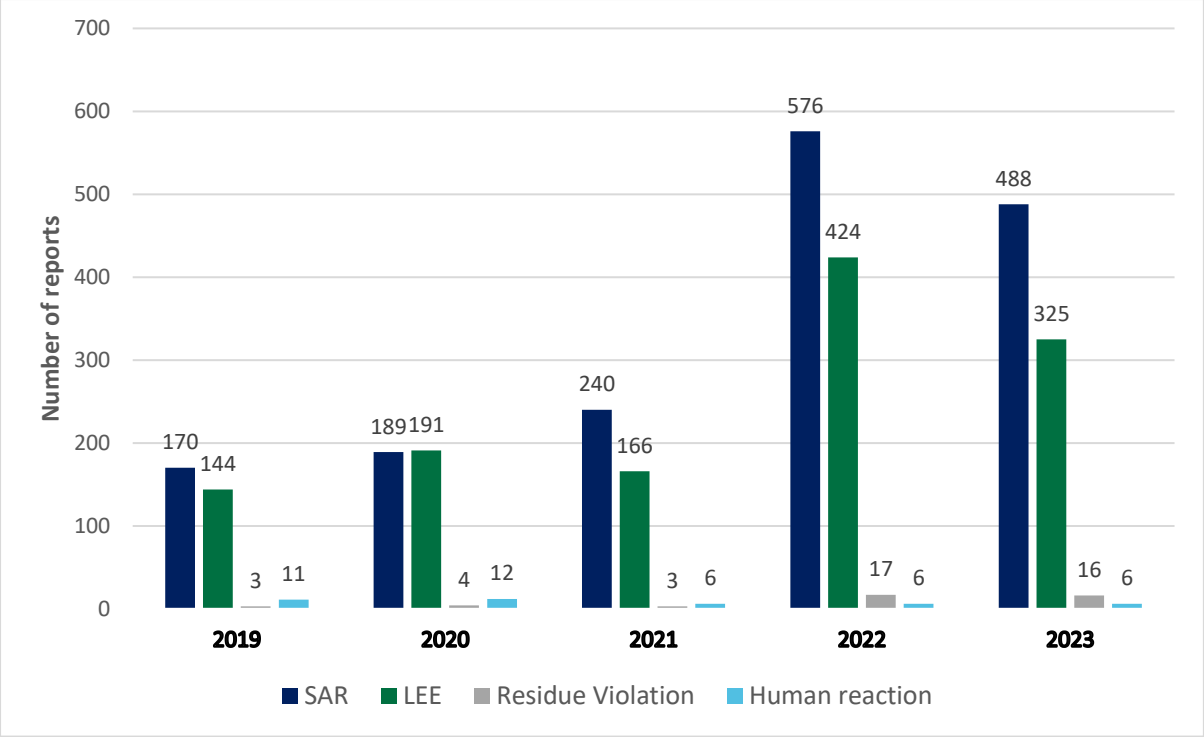


Figure 9 below illustrates a comparison of the number and types of reports received by the HPRA from 2019 to 2021 and recorded in the UPhD from 2022 to 2023.

Figure 9: Number of SAE reports by category from 2019 to 2023



As in previous years, the highest proportion of suspected adverse event reports relates to adverse reactions followed by reports of suspected lack of expected efficacy. The number of reports of possible residue violations as well as the number of reports of suspected adverse reactions in humans is similar this year compared to last year.

Table 7. breaks down the number of adverse event reports received by type of product administered (i.e. animals administered a pharmaceutical product, an immunological product, or animals administered both a pharmaceutical and an immunological product at the same time).

Table 7. Number of AER per type of product in 2023

AERs involving pharmaceutical products only	455
AERs involving immunological products only	359
AERs involving both pharmaceutical and immunological products	21
TOTAL:	835

Just over 54% of all adverse event reports were associated with administration of a pharmaceutical product whereas approximately 43% were associated with administration of an immunological product. Table 8 below summarises the number and type of reported products (both pharmaceutical and immunological) involved in adverse reaction reports in animals and humans in 2023. As outlined in the table, the most frequently reported product types involved in adverse reactions in 2023 were injectable products followed by products for oral administration. This was similar to findings in 2022. It is important to note that multiple product types can be included in the same report (i.e. more than one product

administered to the same animal at the same time), so the total below does not equate to the total number of reports.

Table 8. Number of suspected adverse reactions by product type in 2023

Type of product	Number of reports
Injectable	308
Oral	112
Intramammary	5
Topical	53
Other	16
Total	**494**

2.2. Adverse reactions following human exposure

Six reports of human exposure to VMPs were received during 2023. Five of these reports were received following exposure to immunological products and one report arose from exposure to a pharmaceutical product. The most common clinical symptom reported was injection site swelling following accidental self-injection.

Those administering VMPs are reminded to exercise due caution when handling VMPs and to pay particular attention to avoid accidental self-injection (or indeed accidental exposure to the contents), as well as following 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.

2.3 Reports of lack of expected efficacy

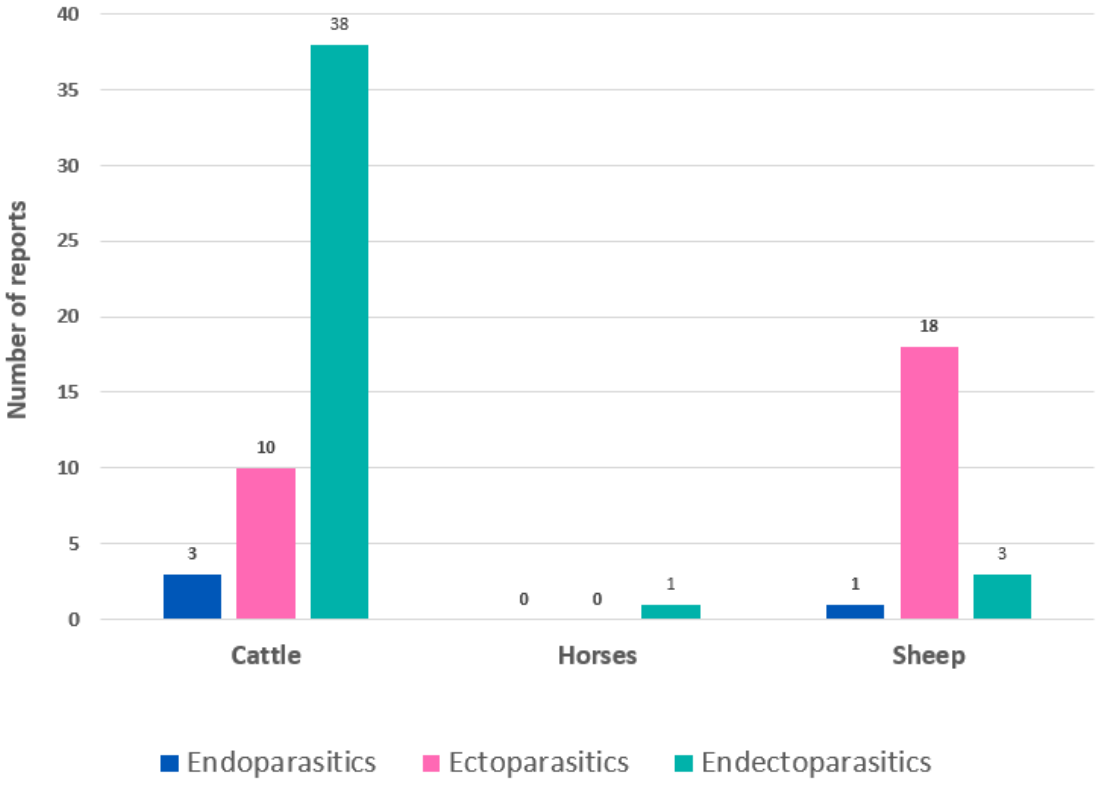
There were 309 reports relating solely to lack of expected efficacy (LEE) reported in 2023.

Of these reports, 177 relate to cattle, 62 relate to dogs, 42 relate to sheep, 15 relate to cats, 6 relate to horses, 2 relate to fish, 2 relate to pigs, 1 relates to chickens, 1 relates to rabbits, and 1 relates to goats.

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 309 reports of suspected LEE, some 52 reports in cattle, 22 reports in sheep and one report in horses were identified by MAHs as LEE following administration of an antiparasitic (endoparasitic, ectoparasitic or endectoparasitic) veterinary medicinal product (Figure 10).

Figure 10: Reports of suspected lack of efficacy following use of antiparasitic products in cattle, sheep and horses in 2023



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 LEE following administration of antiparasitic VMPs. That said, the number of reports of this category of suspected lack of efficacy of antiparasitic products for 2023 (51 in cattle, 1 in horses and 22 in sheep) is similar compared to last year (60 in cattle, 1 in horses and 22 in sheep).

The HPRA published an advisory notice to our stakeholders on 'Reporting of suspected cases of lack of efficacy to wormers and other anti-parasitic veterinary medicines' in March 2023. The purpose of the advisory notice is to encourage the reporting of suspected lack of efficacy. Without reports of lack of efficacy, it is difficult to determine if resistance is developing and if so, whether any change or improvement to the terms of the marketing authorisation is necessary.

2.4 Adverse event reports in relation to intramammary products administered to cattle

One of the objectives of the NVR is to ensure safe and effective use of antimicrobials and to minimise the risk for development of antimicrobial resistance (AMR) within the EU. AMR is a complex global issue and resistance to human and veterinary antimicrobial products has serious health consequences for both humans and animals. The NVR introduced significant restrictions on the use of antimicrobials for prophylactic (preventative) purposes and as a consequence, 'blanket' dry cow therapy with antimicrobials is no longer appropriate. Teat sealant products are licensed for use during the dry period

to prevent the development of new infections. However, using teat sealant products incorrectly can lead to serious consequences for the animal including acute mastitis and death.

A number of reports were received associated with the use of teat sealants in dairy cows at drying off were received, leading to the HPRA publishing a safety advisory notice in February 2023. The notice highlights the importance of following the instructions in order to avoid adverse consequences for animals administered these products. The SPCs and package leaflets of teat sealants have been updated over recent times to ensure consistency of advice to users of these products and in particular, to warn against using such products in cows with clinical mastitis at drying off or as sole therapy in cows with subclinical mastitis at drying off.

Selection of cows for treatment with a teat sealant should be based on veterinary advice. The HPRA will continue to monitor the number of adverse event reports in relation to teat sealants in 2024. Concerning intramammary products generally, there were 16 reports recorded in 2023 of which 9 related to residues in milk, 2 related to lack of efficacy and the remaining 5 were safety reports.

3. European Pharmacovigilance Issues

New measures to reduce risks from exposure to the excipient N-methyl pyrrolidone in veterinary medicines.

As part of pharmacovigilance monitoring, published literature is reviewed to ensure that the benefit-risk profiles of VMPs remain positive. In December 2022, the European Medicines Agency's Committee for Veterinary Medicinal Products (CVMP) recommended updates to the SPCs, labelling and package leaflets of VMPs containing N-methyl pyrrolidone to reduce the risks for women who may handle veterinary medicines containing this excipient and animals that are given these medicines.

The recommendations include warnings for the user, and warnings in relation to pregnancy and fertility. Furthermore, women of childbearing age should exercise caution when using these medicines, and as such a recommendation to wear personal protective equipment such as gloves, particularly for pour-on and spot-on products, shampoos, sprays and concentrates for oral solutions is added.

The Committee also recommended that in the absence of studies demonstrating the safe use of veterinary medicines containing NMP in the target animal species during pregnancy, lactation or lay, NMP-containing veterinary medicines should only be given to animals that are pregnant, lactating, in lay or intended for breeding after assessment of the benefits and risks by the treating veterinarian.

In order to alert users and prescribers to this development, the HPRA published a safety advisory notice on the HPRA website in April 2023 providing details and information on this matter.

In order to remain up to date with most recent developments, readers of this annual pharmacovigilance report are encouraged to register for 'My HPRA' on the HPRA's website in order to receive alerts when such safety advisory notices are published.

3.2 Signal Management

Marketing authorisation holders are required to carry out a signal management process for 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. The signal management process involves multiple steps:

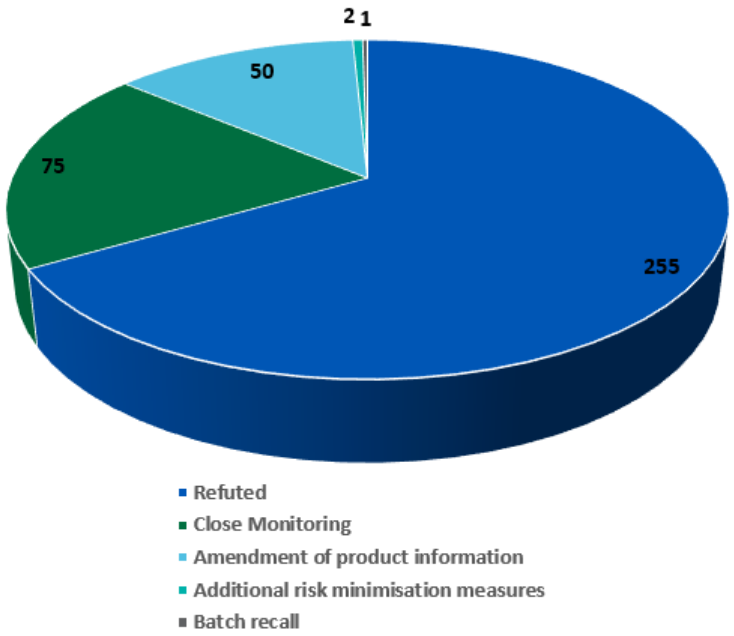
- Detection of any potential signals using a pharmacovigilance database;
- Prioritisation of any potential signals using agreed criteria;
- Validation of the signal due to sufficient evidence demonstrating a new causal association or a new aspect of a known association which justifies further assessment of the signal;
- Assessment of the signal and a decision on the need for any regulatory action.

The outcome of signal assessment will involve one of the following:

- The signal is refuted (a potential causal association is unlikely at present, and no further action is required, however routine pharmacovigilance monitoring should be continued).
- The signal is closely monitored (no action is required at present, but the signal should not be closed and the MAH should assess the signal again at the next due date).
- The signal is identified as a new risk and a proposal for regulatory action is made (e.g. update to the product information, such as the addition of a new adverse event, a change to the frequency reported for an existing adverse event, or the inclusion of additional user safety warnings.).

The outcomes of signals submitted by MAHs to the UPhD in 2023 are indicated below (Figure 11).

Figure 11: Outcome of signals submitted to the UPhD by MAHs in 2023



A pilot signal management expert group (P-SMEG) was established by the European Medicines Agency in collaboration with national competent authorities. The aim of the group is to co-ordinate the signal management process across the EU. The group is composed of delegates from both the EMA and NCAs,

and the HPRA is represented at and actively contributes to this group. In 2023 a total of 82 signals were assessed by the HPRA on behalf of the EU network.

4. Achievements

During 2023, the HPRA pharmacovigilance team delivered on a number of key initiatives, which included:

- 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 September 2023 at which presentations were made outlining the veterinary pharmacovigilance and signal management processes for MAHs.
- Processed 11 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 2 variations applications to update the product information to implement MAH's signal management process in accordance with the NVR.
- Processed 145 variation applications in order to update the reference number and location of the pharmacovigilance system master file (PSMF) in the Union Product database.
- Processed 99 variations to update the information for the qualified person responsible for pharmacovigilance (QPPV) in the Union Product Database.
- Participated in preparation, planning and conducting pharmacovigilance inspections aimed at ensuring compliance with regulatory requirements.

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 emailed to vetsafety@hpra.ie.

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