



anses

Post-MA Surveillance of veterinary medicinal products

2022 Annual Report

October 2023



INVESTIGATE, EVALUATE, PROTECT

**Post-MA surveillance of veterinary
medicinal products**

2022 Annual Report

French Agency for Veterinary Medicinal Products (ANMV)

October 2023

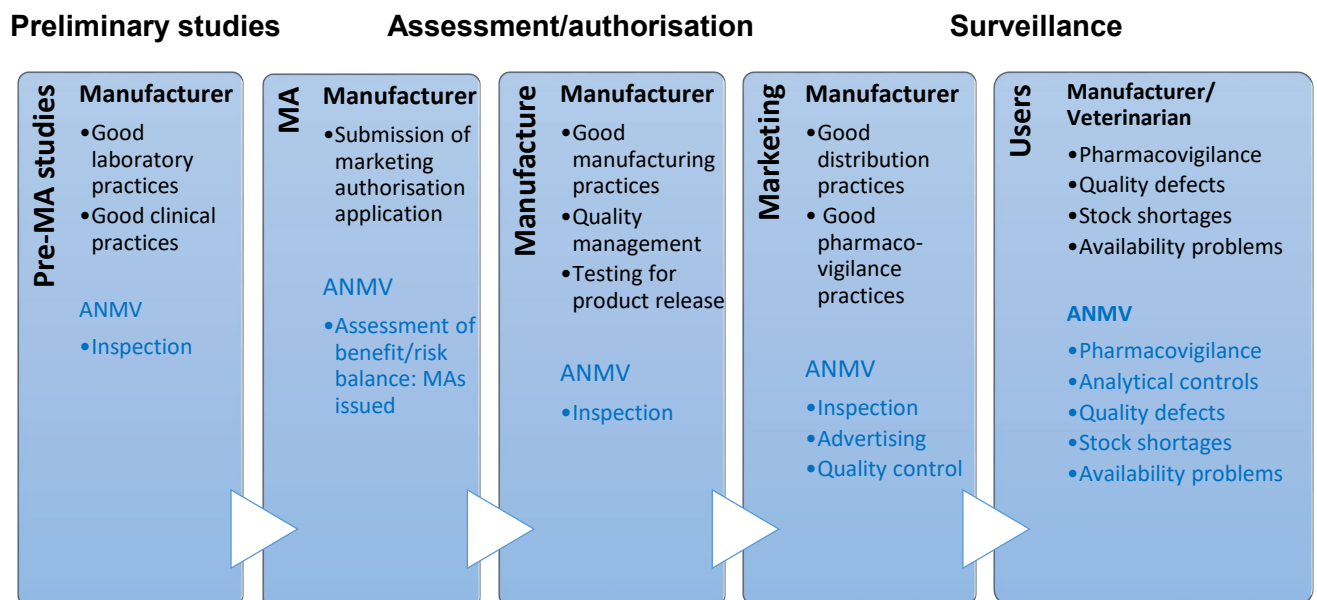
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A/ ANSES and post-MA surveillance of veterinary medicinal products

Veterinary medicinal products are mainly governed by European regulations. ANSES, through the French Agency for Veterinary Medicinal Products (ANMV), is the competent authority for assessing and managing risks associated with veterinary medicinal products in France. Its missions are carried out as part of a European network led by the European Medicines Agency (EMA).

The ANMV, which is part of ANSES, is responsible for ensuring that prescribers and animal owners are provided with veterinary medicinal products that are safe, effective and of good quality. In order to fulfil this task, the Agency intervenes at all stages of the veterinary medicinal product lifecycle:

- **It assesses** national or European marketing authorisation (MA) applications for veterinary medicinal products and takes part in the assessment of European dossiers on maximum residue limits (MRLs) of veterinary medicinal products in foods of animal origin. Prior to assessing applications, it can intervene as early as the medicine testing phase by inspecting the laboratories implementing the trials.
- **It grants** MAs for medicinal products, and authorises clinical trials of these products and the opening of pharmaceutical establishments (licensed operators known in France as *exploitants*, wholesalers, manufacturers, exporters and/or importers of veterinary medicinal products). It certifies imports and exports of veterinary medicinal products.
- Once a medicine has been brought to market, **the Agency monitors** the occurrence of any adverse effects resulting from its use, as well as problems of availability on the French market. It controls quality through testing, analysing reports of quality defects and verifying advertising materials on veterinary medicinal products. It also monitors the operation of pharmaceutical establishments and other industrial veterinary organisations.



Once veterinary medicinal products have been granted authorisation, surveillance involves:

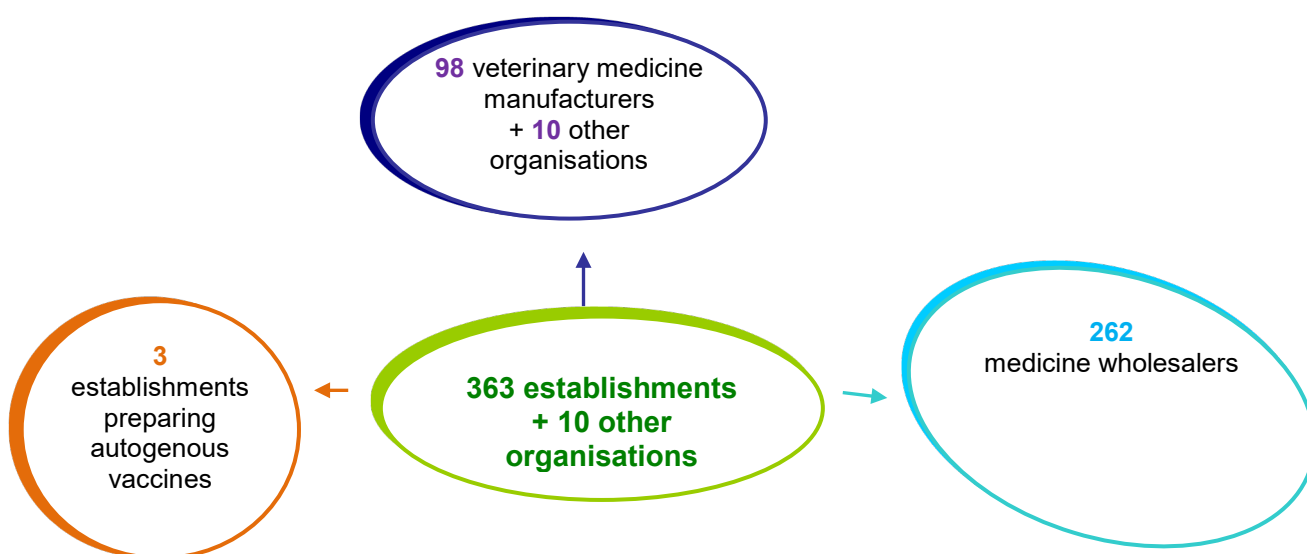
- **Inspecting pharmaceutical establishments** and other veterinary organisations falling within the scope of ANSES-ANMV inspections, to ensure the quality, safety and efficacy of medicines developed, manufactured and distributed in France (Chapter B);
- **Market surveillance**, which includes monitoring of veterinary medicinal product quality through expert appraisals and management of quality defects, analytical control of veterinary medicines, verification of labelling and advertising, as well as monitoring of stock shortages (Chapter C);
- **Monitoring adverse effects** through veterinary pharmacovigilance (Chapter D).

This report covers all the results related to the surveillance of veterinary medicinal products marketed in France for 2022.

B/ Inspection activities

As of 31 December 2022, an authorisation had been issued for one or more activities (manufacture and/or wholesale distribution) to **363 veterinary pharmaceutical establishments**. This figure is stable compared with previous years.

Breakdown of veterinary pharmaceutical establishments in France subject to inspection in 2022, according to their main activity.



In addition to these authorised establishments, ANSES-ANMV also has monitoring and control responsibilities. This relates on the one hand, to MA holders, their representatives and the organisations to which they subcontract some of their activities (advertising, pharmacovigilance, etc.); and on the other hand, to organisations involved in non-clinical studies (test facilities carrying out safety trials), clinical studies (facilities and sites involved in clinical trials) and certain veterinary medicine manufacturing operations (radiosterilisation sites, quality control laboratories).

To ensure access to safe, effective and good quality veterinary medicinal products, the ANSES-ANMV surveillance scheme relies heavily on inspections of pharmaceutical establishments and other veterinary organisations.

Besides national inspections, ANSES-ANMV also conducts inspections of manufacturers outside the European Union that are involved in the manufacture of medicinal products authorised in France.

It is important to ensure that these manufacturers have implemented European good manufacturing practices, since the level of practices in some third countries is not always up to European standards.

These regular inspections, whose frequency is determined by a risk analysis, ensure that pharmaceutical and other veterinary organisations implement quality practices in accordance with the applicable regulations and best practices, enabling these facilities to maintain their certifications throughout the medicinal product lifecycle.

The annual inspection plan is based on a risk analysis that mainly takes into account regulatory requirements, the results of previous inspections (compliance history), the intrinsic risk associated with the activities carried out by the pharmaceutical establishment or veterinary organisation, any reports received, requests from internal or external sponsors, and any campaigns on a given topic. It also takes into account the available inspection resources at the ANMV (the number of inspectors fell from six to five in 2022).

This plan defines a "List 1" of priority establishments, as well as a "List 2" of lower priority establishments.

Because of the health context due to the COVID-19 epidemic, travel over the 2020-2021 period had been either limited (nationally) or ceased completely (internationally), resulting in a backlog in the inspection programme for these two years, which was carried over into the 2022 programme. In 2022, while there were no restrictions on domestic travel, international travel did not resume until May. This return to a normal travel situation meant that work could begin to reduce the backlog.

In the end, 66% of the establishments on List 1 (53 out of 81) were inspected, and seven missions on List 2 were carried out.

Regarding List 1 of the 2022 programme, 28 of the initially planned missions (34%) could not be carried out during the year:

- 15 concerned sites that had already been inspected by the ANMV in the previous five years;
- 13 concerned new sites falling within ANSES's remit.

There are various reasons why these were not carried out: closure of the establishment or construction delays, extension of the validity period of GMP certificates from third countries following COVID restrictions, national legislation pending, etc.

Twenty-two of these 28 unfulfilled missions have been carried over into the 2023 programme.

In addition, the annual inspection plan always includes the possibility of carrying out unannounced visits if necessary. In 2022, by decision of the ANMV management, no unannounced visits were carried out.

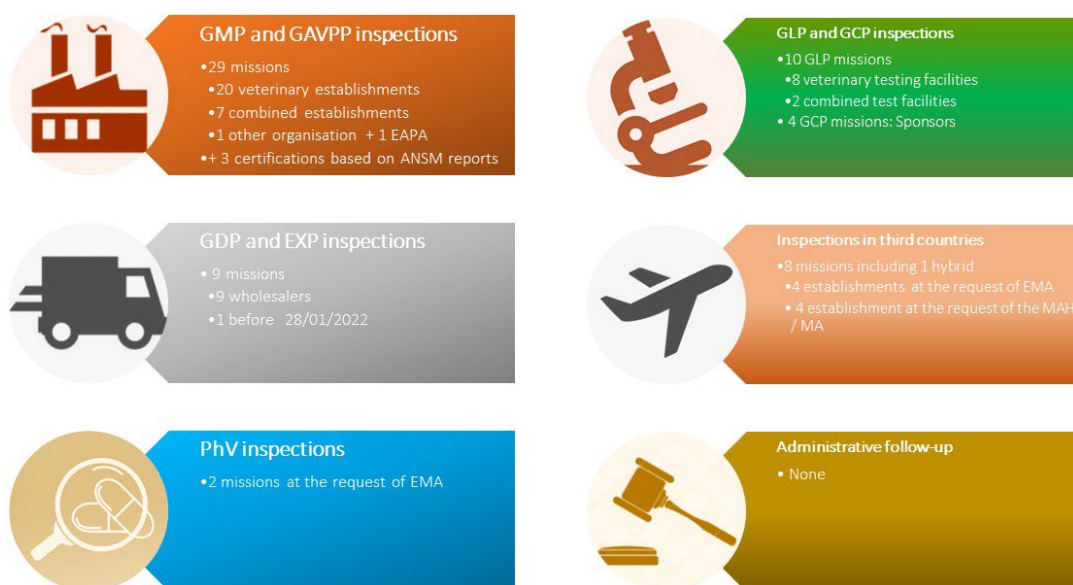
Lastly, two missions were carried out to meet unplanned requests for urgent health inspections or investigations.

In addition, eight GMP inspections of establishments located in third countries were carried out, including four at the request of the EMA.

Key inspection figures from 2022



Review of activity in each inspection area in 2022

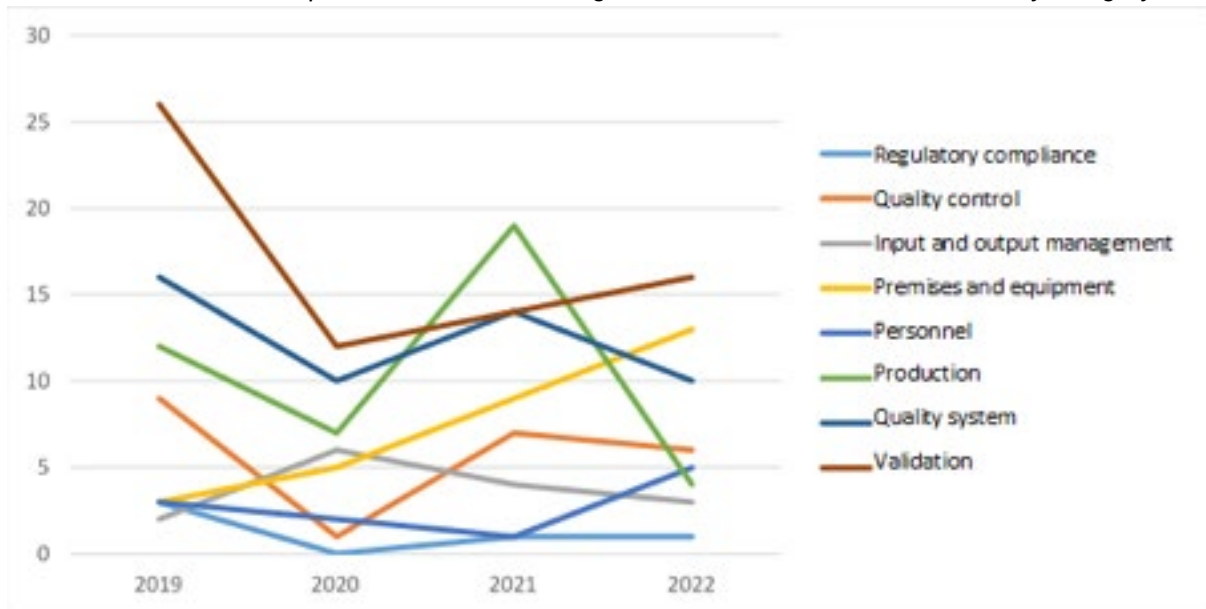


(GMP: Good manufacturing practices, GAVPP: Good autonomous vaccine preparation practices, EAPA: establishment authorised to prepare autogenous vaccines GDP: Good distribution practices, EXP: *exploitant*, PhV: pharmacovigilance, GLP: Good laboratory practices, GCP: Good clinical practices)

The **2022 review** of inspections shows:

- Among manufacturers of veterinary medicinal products, the main areas of discrepancy remained more or less the same. They concerned validation (of processes, cleaning and equipment), the quality system (management of deviations and preventive and corrective measures), production (environmental monitoring, documentation and production control) and quality control (sampling, microbiological testing, etc.).

Breakdown of discrepancies observed among manufacturers from 2019 to 2022 by category



- For wholesalers, the points requiring attention related to schemes for monitoring and improving quality, mainly regarding cold-chain management, handling and following up non-compliances and complaints, and quality risk management.

Two inspections of the pharmacovigilance scheme took place in 2022 at the request of the EMA. These were carried out on the basis of the new veterinary regulations in force since 28 January 2022. Although of little significance, an initial review revealed a number of shortcomings in the creation of the pharmacovigilance system master file (PSMF), the quality and risk management system and in communication.

As part of veterinary medicine research and development, 28 establishments are registered in the "Testing facility" programme. **Ten good laboratory practice (GLP) inspections**, included in the annual inspection plan, were carried out in 2022. They are designed to verify that good practices are followed when carrying out laboratory tests for non-clinical trials, for the purpose of MA applications. These tests primarily serve to guarantee the safety of the veterinary medicinal products tested.

Four inspections were initiated in 2022 as part of the project on good clinical practice (**GCP**) and assessing the compliance of clinical studies carried out in France. The pilot phase is expected to end in 2023.

No formal notice was served to any of the establishments or organisations visited by ANMV inspectors in 2022.

The 2022 inspection plan, together with the flexibility introduced at European level with the decision to automatically extend the validity of GMP certificates, ensured overall compliance with regulatory inspection frequencies and maintained the validity of certifications issued for veterinary pharmaceutical establishments. In 2022, 62 establishments of all categories were inspected, compared with 72 in 2021, mainly due to the reduction in human resources in the ANMV's inspection unit.

C/ Market surveillance

Market surveillance includes monitoring of veterinary medicinal product quality through expert appraisals and management of quality defects, analytical control of veterinary medicines, and verification of labelling and advertising. This also concerns the legal classification of products and the monitoring of stock shortages.

C1 – Quality defects

In 2022, 60 quality defects were recorded and assessed. This places 2022 well below the usual range of reports of quality defects, which fluctuate between 80 and 100 per year (this figure was 91 in 2021).

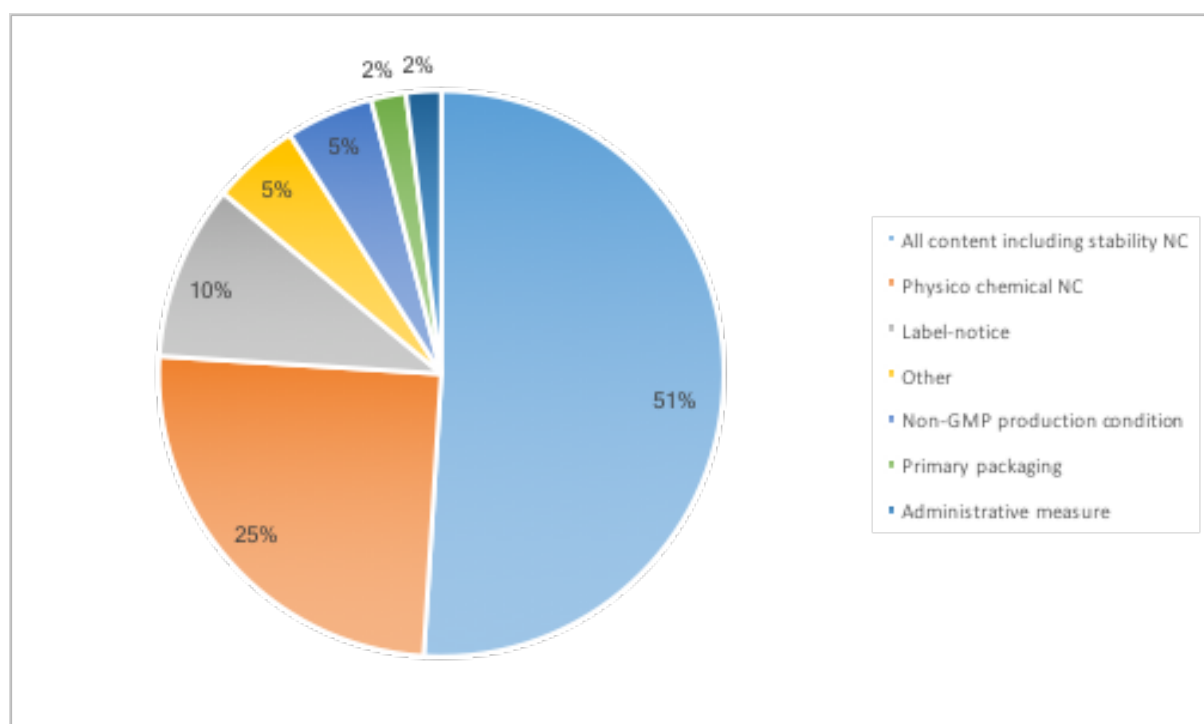
The majority of reports still came from companies.

As in previous years, most quality defects concerned non-compliance with specifications in terms of active ingredient content or other physico-chemical specifications (76%). These non-compliances were mostly discovered while monitoring stability studies of medicines.

It should also be noted that the proportion of these non-compliances relating to specifications has been growing over the last five years, increasing from less than 50% of reports in 2018 to more than 75% in 2022.

The breakdown is shown in the figure below:

Breakdown of quality defects monitored in 2022



(NC = non-compliance; GMP = good manufacturing practices)

Each quality defect undergoes a risk analysis that takes into account the severity of the harm caused, the probability of its occurrence and all the factors specific to the case in question: whether or not harm has actually been observed in the field, marketing of the batches concerned, detectability of the defect, etc. The resulting score is used to classify the risk level, which determines the appropriate level of recall – ranging from no recall through to the public being informed.

Batch recalls involve the withdrawal of a batch of non-compliant veterinary medicinal products already on the market. This withdrawal may be limited, i.e. it may concern only certain stages of the distribution channel (e.g. wholesale distribution), certain distributors or users, or certain specific batches.

The risks posed by the quality defects reported in 2022 were mostly assessed to be minor, and as a result only 12% (n=7) of these quality defects led to batch recalls.

Of the **seven batch recalls in 2022**, only one went as far as the veterinary practitioner stage. Two were limited to the manufacturer-depository level, and four to the wholesale distribution level.

C2 – Analytical quality control of veterinary medicinal products

Selected veterinary medicinal products are subject to analytical control according to an annual programme. It is drawn up on the basis of a risk analysis and in such a way that it is representative of all therapeutic categories and dosage forms, and also covers the vast majority of different veterinary sectors, over a 10-year cycle.

This list of veterinary medicinal products is then supplemented by requests from other ANSES-ANMV departments (scientific assessment, pharmacovigilance, quality defects monitoring, analytical non-compliance monitoring) or from the field. In addition, a rating grid for medicinal products is now available in Europe for classifying these products in terms of their risk levels. The veterinary medicinal products rated and identified as posing the greatest risk are also included in the annual control programme.

In 2022, **116 batches of medicinal products were analysed with 568 tests carried out mainly by the ANMV laboratory**. Some tests that could not be performed by the ANSES-ANMV laboratory were carried out by other laboratories in the European Network of Official Medicines Control Laboratories (OMCL Network).

Two medicines were found not to comply with the MA specifications, i.e. a non-compliance rate of 1.8% (compared with 4.8% in 2021).

The identified non-compliances related to labelling anomalies.

C3 – Advertising control

Advertising of veterinary medicinal products is regulated by Regulation (EU) 2019/6 and by the French Public Health Code (CSP). It only covers authorised veterinary medicinal products. **Advertising to the public is only permitted for non-prescription medicinal products**. Depending on the type of medicinal product and/or the recipient, advertising materials are **subject to either authorisation, or simply prior declaration**. For more information, a guide to good advertising practices is available on the ANSES website¹. **A new version of this guide was published in August 2022**.

Advertisements requiring prior authorisation concern antimicrobials, medicinal products subject to a risk management plan, medicinal products indicated for regulated diseases, and medicinal products containing anabolic, anticatabolic or β -agonist substances. Lastly, authorisation is required for the advertising of any medicines intended for the general public.

In 2022, **341 advertising applications led to 991 advertising materials being checked**. This represented a considerable fall of 50% in the number of applications and 42% in the number of advertising materials, compared with 2021.

The breakdown of type of materials has also changed. In 2022, it was as follows: 35% of advertising materials concerned authorisations (with 118 submissions) and 65% concerned declarations (with 223 submissions), whereas the usual trend in previous years was 20% authorisations and 80% declarations. These changes can be correlated with the following elements:

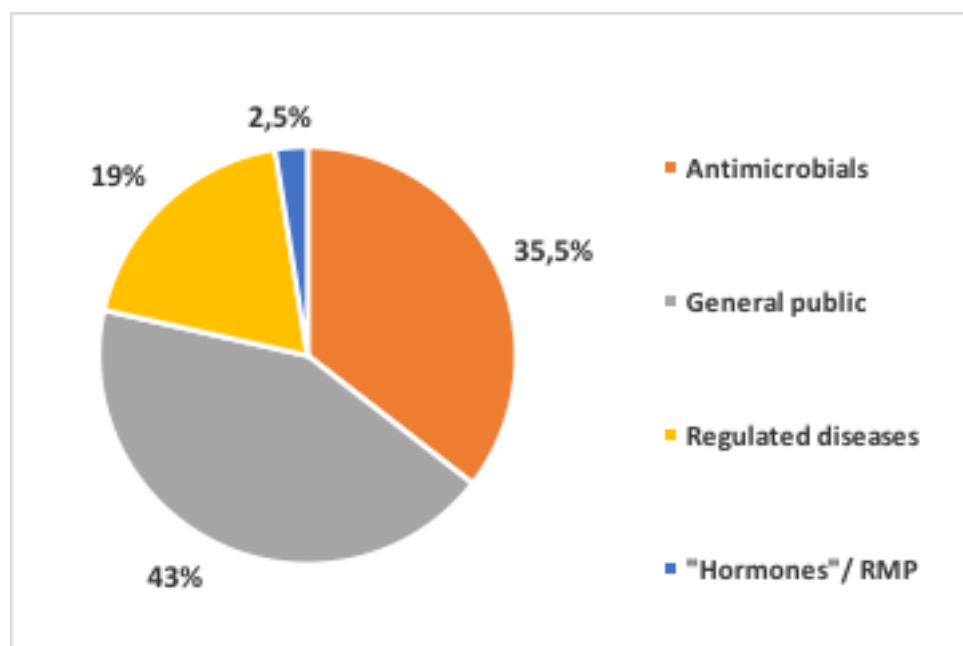
- An increase in the scope of the authorisation requirement due to regulatory changes concerning regulated diseases: this has increased the number of applications submitted for authorisation;
- Publication of a new tax decree on 28/01/2022, introducing a levy on all submissions (concerning both authorisations and declarations), whereas in previous years only those requiring authorisation were subject to a levy.

No refusals of publication were notified in 2022.

The vast majority of applications requiring authorisation concerned medicinal products intended for the general public (non-prescription medicines). Among prescription medicines, the submissions mainly concerned antimicrobials.

¹https://www.anses.fr/fr/system/files/20220808_Guide%20des%20BPP_Anmv_version%20n%C2%B06_v1_ANMV_version%20finale.pdf

Breakdown of advertising applications submitted for authorisation in 2022



(RMP = Risk Management Plan)

C4 – Classification of "borderline" products

ANSES-ANMV carries out work to classify so-called "borderline" products, when notified of such cases or after receiving requests for pre-marketing opinions. Based on the presentations and claims made, this process seeks to determine whether or not the products in question can be defined as veterinary medicines. In many cases, this concerns products on the boundary with biocides or animal feed. This activity has been organised within the Market Surveillance and Pharmacovigilance Unit, and mainly involves use of a generic assessment grid.

In 2022, the ANMV received 77 requests, a number that is stable compared with 2021, **concerning around 350 products**, i.e. 17% more than in 2021. These included 37 cases containing one or more products that were then classified as veterinary medicinal products. They gave rise to 17 emails requesting that the products be brought into compliance, and one **letter of formal notice concerning the "Traitement Anti-varroa" product offered by the StopVarroa website**. This website was offering a product for sale that fell under the definition of a veterinary medicinal product but had no marketing authorisation, and had therefore not been assessed for its quality, safety and efficacy according to European regulations. The company illegally marketing this unauthorised medicine was located in a third country, illustrating the difficulties faced by the authorities in regulating internet sales.

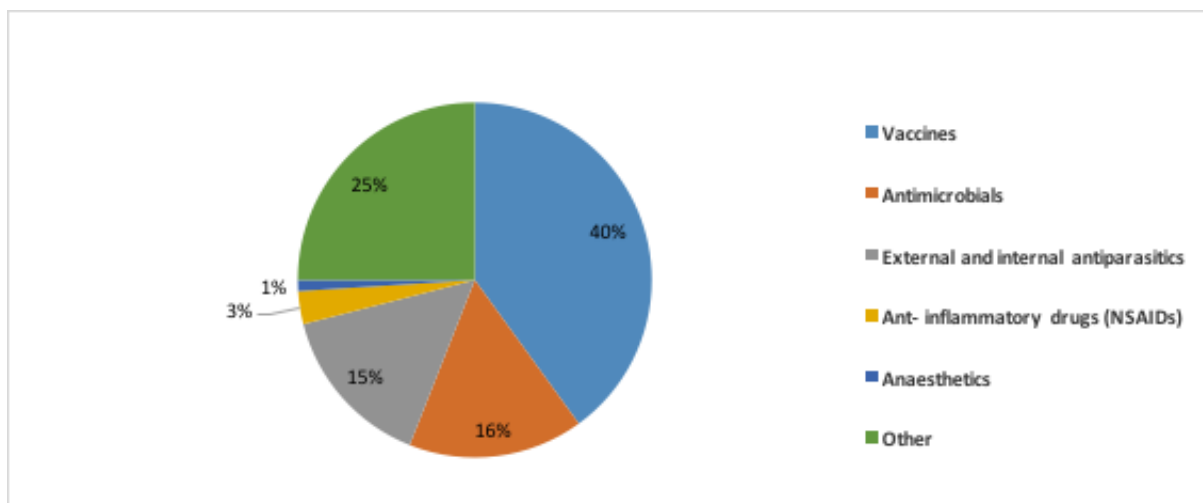
The other requests sought advice on pre-marketing regulations.

C5 – Management of shortages of veterinary medicinal products

Manufacturers marketing medicinal products have a **regulatory requirement to report any supply disruptions to the ANMV**. These reports are used to identify proven stock shortages and their impact on practitioners and animal owners as early as possible, in order for possible alternatives to be identified and information on critical stock shortages to be published.

In 2022, **101 cases of shortages were reported**, a figure that was **40% higher** than in 2021.

Breakdown of stock shortages by type of medicine in 2022



Vaccines were the main category of medicines affected by shortages in 2022. Note that vaccines account for a quarter of the veterinary medicinal products market in terms of purchase volumes, all animal species combined. While vaccines for dogs and cats had been the main products affected by disruption in 2021, the shortages in 2022 concerned all animal species. Horses were also comparatively heavily affected in 2022, due to cumulative shortages of influenza vaccines, whether or not combined with tetanus.

A stock shortage is said to be critical when it could introduce a risk to human health, animal health or animal welfare. The criticality analysis takes into account various criteria: impact of the shortage on human and animal health, other medicines available for the disease in question and their respective market shares, estimated duration of the shortage, economic impact of the shortage on the sector in question (avian, equine, etc.).

In 2022, 24 new critical stock shortages were reported on the ANSES website, compared with six in 2021.

Alternative solutions were systematically sought. In 2022, palliative solutions were found in 16 cases: seven following the release of specific batches (for which the specifications were not entirely in line with the authorisation dossier), seven involving imports or temporary use authorisations granted by the ANMV, and the last two thanks to an extension of the batch shelf life or an accelerated MA amendment procedure. Implementing these solutions avoided any risk to human health, animal health or animal welfare, while maintaining minimum safety criteria.

The Market Surveillance and Pharmacovigilance Unit:

- continued its participation in the working group led by EMA on medicine shortages and unavailability, which meets on a monthly basis;
- continued providing input for the network of single points of contact (SPOC) between EU agencies, with a view to informing and coordinating action between authorities on the most significant shortages (search for alternative solutions for medicines and batches available in other countries, etc.).

D/ Pharmacovigilance

D1 – 2022 review

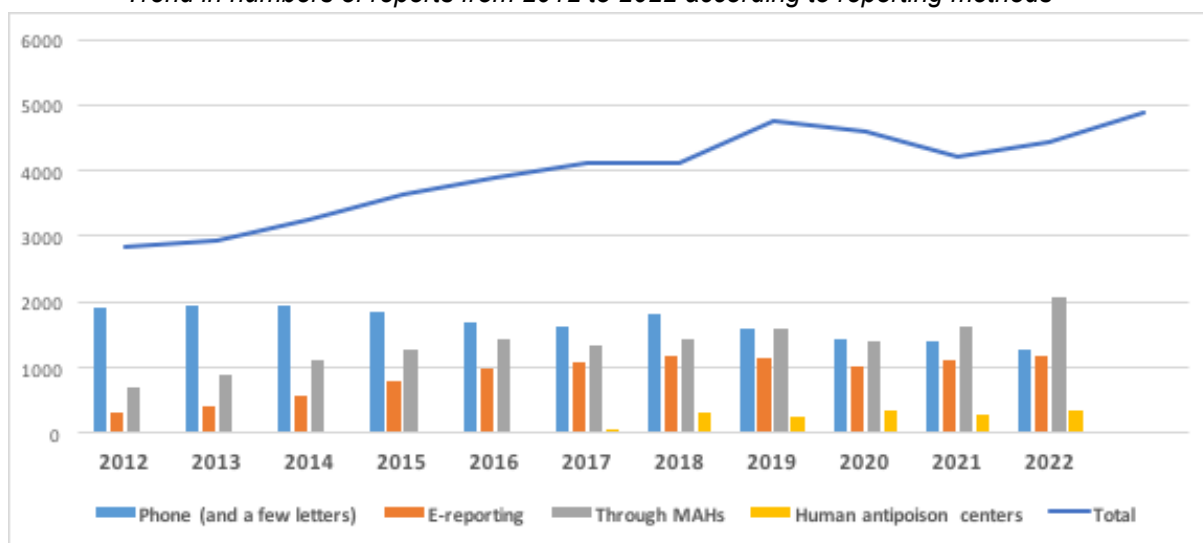
- Trend in total numbers of reports of adverse effects

In 2022, 4887 pharmacovigilance reports were notified to ANSES, representing a 10% increase in the total number of reports compared with 2021.

This sharp rise does not reflect a real increase in reports from the field, but rather a change in the way cases received by MA holders are transmitted to the ANMV: until the end of September 2022, only cases received by MA holders that were classified as serious were registered by the ANMV, whereas **since October 2022, all cases received by MA holders, both serious and non-serious, have been recorded by the ANMV** in the national veterinary pharmacovigilance database. Thus, if the 505 non-serious cases from MA holders recorded since October 2022 are removed from the total of 4887 reports, to obtain a number comparable to that of 2021, there is no increase in the total number of reports of adverse effects in 2022 compared with 2021 (in fact there was a slight decrease of -0.85%).

These 4887 reports recorded in 2022 correspond to adverse effects occurring in animals or humans following the use of a veterinary medicinal product, as well as adverse effects occurring in animals following administration of a medicinal product designed for human use (excluding accidental ingestion).

Trend in numbers of reports from 2012 to 2022 according to reporting methods



Human antipoison centres: human cases reported to the ANMV by French poison control centres; MAHs: reported to marketing authorisation holders.

Of the 4887 reports received, 4510 concerned animals and 377 related to humans. The majority of reports relating to humans came from poison control centres (91%). As for the cases concerning animals transmitted directly to the ANMV and the CPVL², veterinarians remained the main sources of reports (90%).

² See glossary.

As in previous years, the breakdown of the reports by type of reported adverse effect reveals a vast majority of reports concerning adverse effects in the strict sense of the term in animals (72% of the total number).

Types of adverse effects reported in 2022

| Type of effect | Number | % |
|-----------------------------------|---------------|------------|
| Adverse effects in animals | 3529 | 72 |
| Lack of efficacy | 959 | 20 |
| Residue issues | 22 | 0.5 |
| Environmental issues | 0 | 0 |
| Transmission of infectious agents | 0 | 0 |
| Adverse effects in humans | 377 | 7.5 |
| Total | 4887 | 100 |

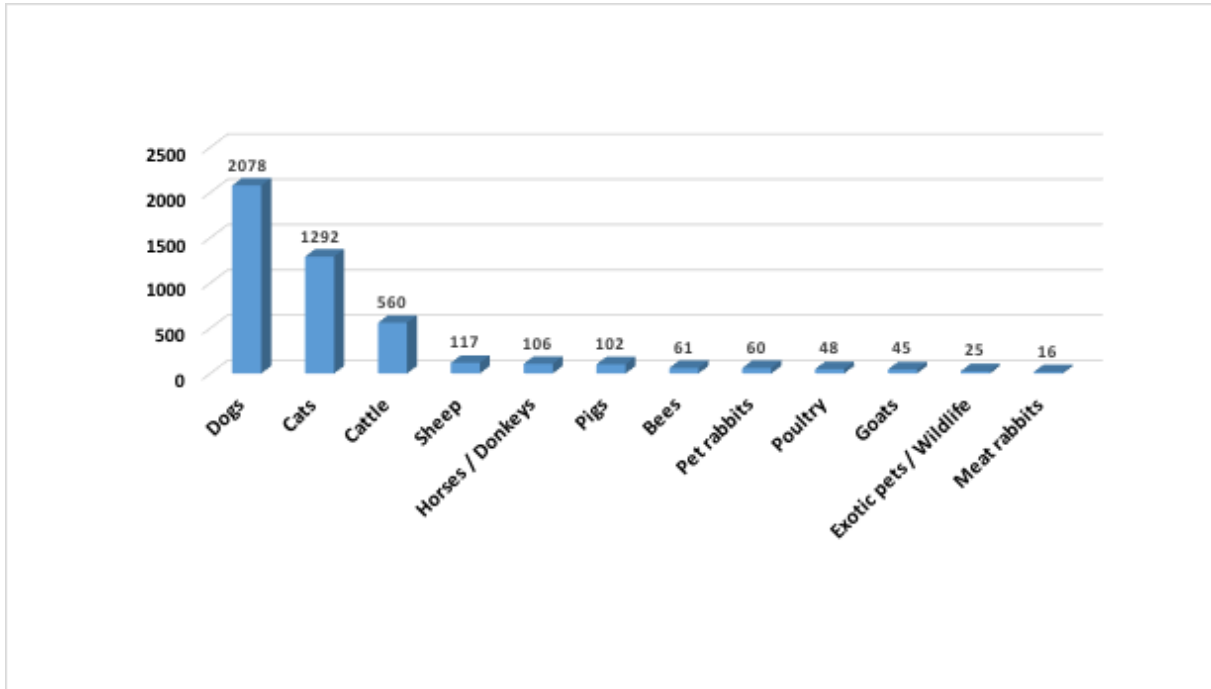
The number of reports of suspected lack of efficacy rose to 20%, whereas it had previously always been below 15%. In principle, this does not reflect a real increase in observations of lack of efficacy in the field, and these higher figures for 2022 can be explained by a number of one-off factors: 56 cases came from studies in the beekeeping sector on the efficacy of medicinal products against varroasis, and 49 cases came from a field study on the efficacy of eprinomectin in sheep. The increase can also be explained by the aforementioned bias due to the recording in the ANMV database of non-serious cases received by MA holders since October 2022, as 207 cases of lack of efficacy classified as non-serious were added to the database in 2022.

A few cases involving suspicions of veterinary drug residues in milk were reported. They involved milk samples declared "positive" for inhibitors under the official method for screening for antibiotic residues in milk. However, in these cases, quantification or identification of the incriminated compound(s) was unavailable, which prevented the causal link from being assessed.

- Reports by species and therapeutic category

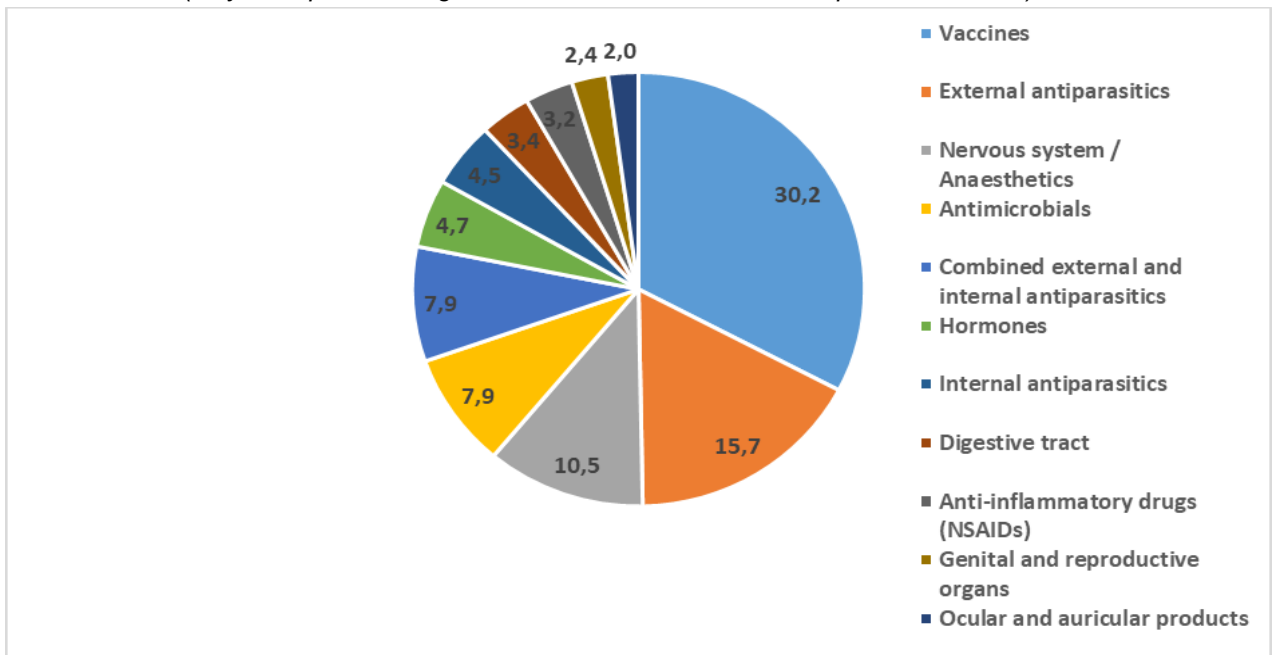
Since a single report may concern several medicinal products, a total of 5906 medicines were involved in the 4887 reports. As in previous years, domestic carnivores again accounted for more than 80% of reports involving animals.

Breakdown of reports by affected species in 2022



Vaccines remained the main products incriminated in an adverse effect in most species. They are also the main therapeutic category marketed, accounting for a quarter of the veterinary medicinal products market in terms of purchase volumes, all animal species combined. However, in bees, external antiparasitics were the most commonly cited, and in exotic pets/wildlife the predominant therapeutic category was internal antiparasitics (endectocides). In sheep, on the other hand, external and internal antiparasitics took over from vaccines this year, following a series of reports emanating from a study on the efficacy of eprinomectin in sheep.

*Breakdown of percentage of reports by therapeutic category cited – 2022
(only therapeutic categories cited in more than 2% of reports are shown)*



Breakdown of reports by therapeutic category and species in 2022

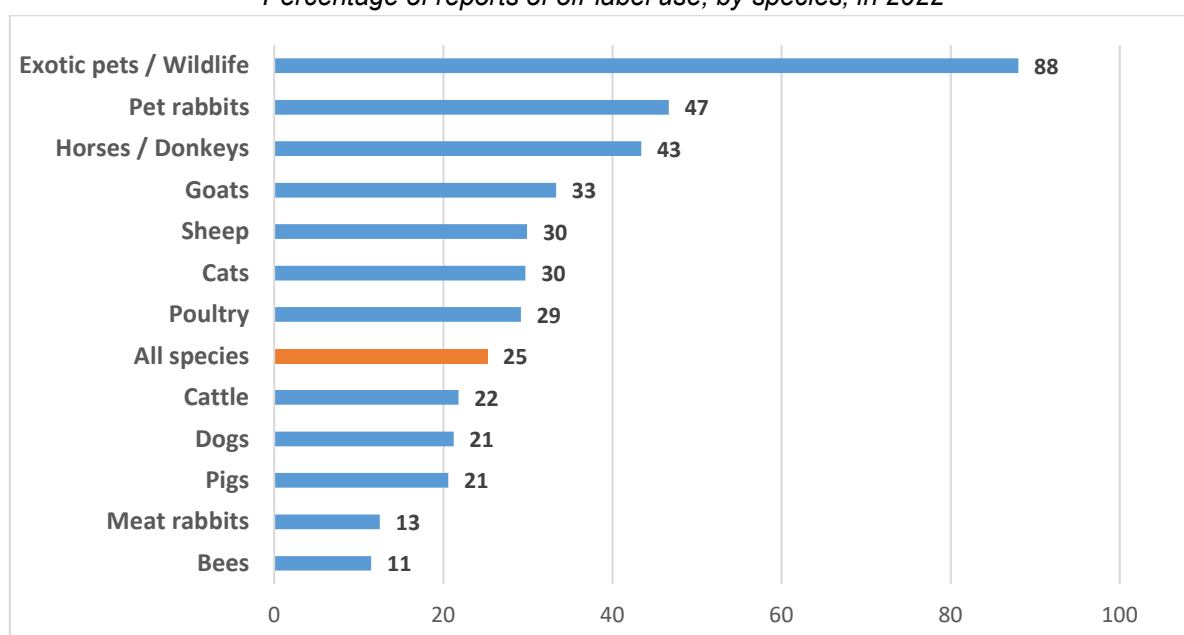
| | Dogs | Cats | Cattle | Horses/Donkeys | Sheep | Pigs | Pet rabbits | Bees | Poultry | Goats | Exotic pets/Wildlife | Meat rabbits | General total |
|---|-------------|-------------|------------|----------------|------------|------------|-------------|-----------|-----------|-----------|----------------------|--------------|---------------|
| Vaccines | 832 | 270 | 387 | 40 | 49 | 98 | 38 | 0 | 50 | 13 | 1 | 8 | 1786 |
| External antiparasitics | 506 | 332 | 10 | 0 | 0 | 1 | 13 | 61 | 2 | 0 | 1 | 0 | 926 |
| Nervous system/Anaesthetics | 347 | 190 | 23 | 31 | 1 | 5 | 16 | 0 | 0 | 3 | 5 | 0 | 621 |
| Hormones | 148 | 100 | 14 | 7 | 0 | 7 | 0 | 0 | 0 | 0 | 3 | 0 | 279 |
| Antimicrobials | 116 | 63 | 223 | 35 | 5 | 5 | 5 | 0 | 3 | 4 | 4 | 1 | 464 |
| Combined external and internal antiparasitics | 105 | 232 | 32 | 8 | 67 | 0 | 4 | 0 | 0 | 16 | 0 | 0 | 464 |
| Internal antiparasitics | 98 | 81 | 37 | 6 | 10 | 3 | 2 | 0 | 5 | 15 | 10 | 0 | 267 |
| Genital and reproductive organs | 98 | 15 | 21 | 1 | 0 | 4 | 0 | 0 | 0 | 0 | 1 | 0 | 140 |
| Anti-inflammatory drugs (NSAIDs) | 96 | 31 | 35 | 18 | 0 | 5 | 0 | 0 | 0 | 1 | 4 | 0 | 190 |
| Digestive tract | 95 | 61 | 46 | 4 | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 211 |
| Ocular and auricular products | 78 | 38 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 117 |
| Cardiovascular and circulatory system | 54 | 38 | 12 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 105 |
| Dermatology | 45 | 15 | 0 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 64 |
| Antineoplastic and immunomodulator agents | 22 | 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 38 |
| Blood and blood-forming organs | 4 | 3 | 4 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 13 |
| Respiratory system | 3 | 2 | 3 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 13 |
| Other | 134 | 62 | 0 | 9 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 208 |
| General total | 2781 | 1549 | 847 | 168 | 136 | 129 | 85 | 61 | 60 | 52 | 29 | 9 | 5906 |

* The medicine category "Other" includes allergy products, homeopathic drugs and medicinal products for human use.

These breakdowns by species or therapeutic category were calculated on the basis of all the reports recorded in the national database, without taking into account the type of report or conditions of use of the medicinal products (whether or not they complied with the summary of product characteristics – SPC).

In 2022, off-label uses of veterinary medicinal products again accounted for a quarter of all reports. Unsurprisingly, the highest proportion of reports following off-label use came from "minor" species (with the exception of bees and meat rabbits), due to the use of medicines authorised for other target species. In addition, cases continued to be reported in pet rabbits following the mistaken administration of medicines containing fipronil, which are contraindicated in this species. In sheep, cases were dominated by reports of lack of efficacy after oral administration of pour-on eprinomectin. In cats, the most common off-label reports concerned permethrin poisoning, oral administration with pipettes and overdose of milbemycin oxime/praziquantel. In dogs, overdoses predominated (antiepileptics, antibiotics, antiparasitics), followed by accidental ingestions (of collars, or medicines intended for horses).

Percentage of reports of off-label use, by species, in 2022



- MA amendments

The pharmacovigilance reports and their analysis, at either national or European level, enable the SPCs to be amended to include any new information obtained.

These amendments concerned 53 medicines in 2022, compared with 71 in 2021. Assessment of the pharmacovigilance data mainly led to the "Adverse reactions" section of the SPCs being supplemented, with the addition of new clinical signs or changes to the frequency of their occurrence, but also enabled new warnings, contraindications and precautions for use to be added.

These changes are made public via the ANMV's digital newsletter published on the ANSES website, to which readers can subscribe [here](#) (in French).

For centralised MAs, the recommendations for updating SPCs are available on the EMA website³.

³ https://www.ema.europa.eu/en/documents/other/pharmacovigilance-related-regulatory-recommendations-centrally-authorized-veterinary-medicinal_en-0.pdf

D2 – Communication on veterinary pharmacovigilance

In order to promote pharmacovigilance, the ANMV produces summaries of reported cases, relating to a specific medicine, therapeutic category and/or species, and publishes position papers on ways to facilitate and improve the quality of reporting. This information is disseminated via different media, such as the www.anses.fr/en website, the digital newsletter of the National Council of the French veterinary statutory body (CNOV), the trade press and congresses. A video presentation has also been posted online to facilitate the electronic submission of reports of adverse effects⁴.

In addition, the ANMV promotes research and thesis work in the field of veterinary pharmacovigilance by providing access to the data in the national pharmacovigilance database. In 2021, following the introduction of new provisions in favour of open science, the Agency began placing "author versions" of its articles on both the institutional open archive site ([HAL Anses](https://hal.anses.fr)) and the [Veterinary medicinal products](#) page of the ANSES website, six months after their publication in journals.

- Articles and press releases

Articles on pharmacovigilance published in 2022 included a review of adverse effects reported in humans following exposure to veterinary medicines (*La Semaine Vétérinaire* No. 1965, 11 November 2022). Another review concerned clustered cases of hypersensitivity in cattle following injections of various antibiotics (*La Dépêche Vétérinaire* No. 1606, July 2022). Two articles were also published in the pharmacy trade press to reiterate certain precautions concerning external antiparasitic treatments for pets (*Le Moniteur des Pharmacies* No. 3429, July 2022), and on the adverse effects of human topical hormone treatments on pets (*Le Moniteur des Pharmacies* no. 3402, January 2022).

Following the introduction of new risk management measures concerning oral contraceptives intended for domestic carnivores, a press release for the general public was also published on the ANSES website, along with two articles in the veterinary and pharmacy trade press.

Two communications also shared pharmacovigilance signals detected at European level with a domestic audience. The first warned of an increase in the frequency of hypersensitivity reactions in cattle following vaccination with Hiprabovis IBR Marker Live (a signal detected by the Belgian agency), and the second provided information on the risks to avian scavengers of medicines containing flunixin-meglumine (*La Dépêche Vétérinaire* No. 1628, October 2022).

In order to promote good reporting practices, the ANMV continued its awareness-raising campaigns targeting a specific sector (beekeeping in this case): posting online recommendations for reporting any suspected lack of efficacy against *Varroa destructor*⁵ and publishing an article in the November issue of the *Bulletin des GTV* on good practice when using medicines against *Varroa destructor*.

In 2022, two new communication tools for the general public were produced: a video broadcasting messages on preventing risks of external antiparasitics for pets was created and provided to pharmacies, and an infographic with a reminder of good practices in the use and storage of veterinary medicines was published on the ANSES website.

The ANMV continued its monthly publication of clinical cases in the *Dépêche Vétérinaire*, which began several years ago. Cases are selected for their potential interest to the veterinary profession. A description of each clinical case is supplemented by the pharmacovigilance specialist's analysis of the

⁴ <https://www.youtube.com/watch?v=QcnSnoOCskE&feature=youtu.be>.

⁵ <https://www.anses.fr/fr/system/files/Comment%20de%CC%81clarer%20un%20manque%20d%27efficacite%CC%81%20varroa%20ANMV%20VDef.pdf>

possible relationship between the administered medicine(s) and the clinical sign(s) observed subsequently, as well as the resulting causality score.

A list of articles published by the ANMV in 2022 is available on the Veterinary Medicine page of the ANSES website⁶ and is provided in the annex to this report.

- Participation in congresses

ANSES-ANMV regularly discusses veterinary pharmacovigilance when participating in congresses such as the national meetings of the veterinary technical groups (GTVs) and the annual congresses of the French Association of Veterinarians for Companion Animals (AFVAC) and the French Equine Veterinary Association (AVEF).

For example, at the national AFVAC congress in 2022, the Agency presented a summary on adverse effects of veterinary medicinal products on humans, the circumstances in which they occur and how to prevent them, along with a review of adverse effects of monoclonal antibodies. At the AVEF, two posters were presented, one on pharmacovigilance concerning new cell therapies, and the other on vaccination failures against equine influenza based on data from the Epidemiological surveillance network for equine diseases (RESPE). The pharmacovigilance scheme was presented to the veterinarians belonging to the "Réseau Cristal" association during the session on the "Alterbiotique" solution for calves, and a review on clustered cases of hypersensitivity in cattle following injections of various antibiotics was presented at the GTVs' meeting in Brittany. Lastly, at the national meetings of the GTVs, a presentation was given on cases of lack of efficacy of medicinal products intended for bees and how to report them.

- Internships

ANSES-ANMV regularly hosts trainees with a view to them using pharmacovigilance data for veterinary doctoral theses. For example, in 2022 and early 2023, in conjunction with the Toulouse National Veterinary School, it hosted an internship on the adverse effects of vaccines against leptospirosis on dogs. The results of this work will be presented at the AFVAC congress in 2023.

E/ Outlook for 2023

Following the entry into force of Regulation (EU) No 2019/6 on veterinary medicinal products on 28 January 2022, national regulations need to be revised accordingly. While the Order of 23 March 2022 established the legislative framework, a number of decrees, ministerial orders and decisions need to be reviewed and/or drafted.

In particular, the changes concerning post-MA monitoring now include a broader scope for inspections, with checks on all players subject to obligations under the regulation, even if they are not required to obtain authorisation as a pharmaceutical establishment (MA holders, marketing representatives, etc.); and forthcoming controls over registration of homeopathic medicinal products or medicinal products intended for exotic pets, and online sales of non-prescription veterinary medicinal products, under conditions to be set by decree.

At the same time, ANMV staff are continuing their involvement in ongoing European work, in particular with the introduction of signal detection procedures and the revision of good manufacturing practice for veterinary medicinal products.

⁶ <https://www.anses.fr/fr/system/files/Internet%20recap%20com%20ANMV%202022.pdf>

Lastly, in view of the various changes in the regulatory framework applicable to veterinary medicinal products, the ANMV has also had to amend its procedures, methodology and IT tools with effect from 2022.

F/ Summary and conclusions

As part of its post-MA surveillance activities, the ANMV conducted 62 inspections in establishments, representing 624 inspection mission-days.

Reports of quality defects, which have been generally stable in recent years, led to only a few batch recalls (n=7), while analytical controls of veterinary medicinal products found a 1.8% rate of non-compliance.

In pharmacovigilance, the 10% increase in the total number of reports registered was due more to a change in methodology than to a real increase in the number of cases reported. The Agency is continuing its communication campaigns targeting professionals, in order to promote veterinary medicinal product pharmacovigilance.

Shortages mainly concerned vaccines, this year affecting most animal species. These shortages were due to a number of factors, including increased demand, and supply and/or production problems. The ANMV plays a key role in managing these shortages, identifying alternatives when they concern critical medicines. Regarding this issue of lack of availability, it would be advisable to follow the recommendations of the structural reform support programme (SRSP), a project co-funded by the European Union that calls for a "One Health" approach to human health, animal health and the environment. Its aim is to identify and implement pilot measures in France to address the root causes of shortages and lack of availability of off-patent antibiotics used in human and veterinary medicine, while protecting the environment and taking account of the European and national regulatory contexts⁷.

The main prospect for 2023 in the monitoring of veterinary medicinal products is fully in line with ANSES-ANMV's general activity programme and relates to continued implementation of Regulation (EU) No 2019/6, which came into force on 28 January 2022. This mainly involves adapting French regulations and ANSES-ANMV's IT tools to the European databases (especially those for medicinal products and pharmacovigilance).

Lastly, it should be remembered that in terms of transparency, numerous data on veterinary medicinal products are now available on the EMA website. These data, supplied by the various national authorities, provide access to information on all European countries:

- Authorised medicines (<https://medicines.health.europa.eu/veterinary/en>)
- Manufacturing and wholesale distribution establishments (<http://eudragmdp.ema.europa.eu/inspections/logonGeneralPublic.do>)
- Pharmacovigilance reports (<https://www.adrreports.eu/vet/en/index.html>)

2022 figures for post-MA activities

624 inspection mission-days
62 organisations inspected
60 reports of quality defects
7 batch recalls
116 analytical controls of medicines
101 stock shortages reported, including 24 critical
991 advertising materials submitted
77 requests for classification (350 products)
4887 adverse effect reports

⁷ <https://sante.gouv.fr/prevention-en-sante/les-antibiotiques-des-medicaments-essentiels-a-preserver/des-politiques-publiques-pour-preserver-l-efficacite-des-antibiotiques/article/la-france-s-engage-pour-la-disponibilite-des-antibiotiques#Le-Programme-d-appui-a-la-reforme-structurelle-devenu-Instrument-d-appui-nbsp>

- Signals in pharmacovigilance and annual monitoring (<https://iris.ema.europa.eu/signalpd>)

This eighth annual report on activities relating to post-MA surveillance of medicinal products shows that the quantitative results of this work remain fairly consistent from one year to the next. These surveillance activities, carried out by ANSES-ANMV throughout the medicinal product lifecycle, help improve the safety of veterinary medicinal products. Useful changes and adjustments to the scope of the post-MA activities presented in this report are planned, driven by the modernisation of the European legislative framework and the associated tools.

GLOSSARY

- MA: Marketing authorisation
- GCP: Good clinical practices
- GDP: Good distribution practices
- GMP: Good manufacturing practices
- GLP: Good laboratory practices
- GAVPP: Good autonomous vaccine preparation practices
- CPVL: Veterinary Pharmacovigilance Centre in Lyon
- EMA: European Medicines Agency
- Non-EU GMP: Good manufacturing practice outside the European Union
- OMCL: Official medicines control laboratory
- SPC: Summary of product characteristics

ANNEX: information published on anses.fr in 2022

Pharmacovigilance – Alerts and press releases

- Clustered cases of type 1 hypersensitivity reactions in cattle following the administration of antibiotics: update on the situation in December 2021
- Cases of bovine neonatal pancytopenia: consider the treatments administered to the mothers
- Hormonal treatments for humans applied to the skin can lead to adverse effects in pets
- HIPRABOVIS IBR MARKER LIVE – increased incidence of anaphylactic reactions in cattle
- Dog deworming: pay attention to certain breed particularities
- Birth control pills for female cats and dogs are medicines that must be prescribed by a veterinarian
- Use of alpha2-agonist anaesthetics in the Pomeranian: no particular contraindication in healthy dogs
- Live attenuated vaccines administered intra-nasally in dogs: a reminder of precautions for use to avoid any human contamination
- Prascend for horses: alert regarding cases of accidental human ingestion

Pharmacovigilance – Studies and reviews

- Treatment of allergic dermatitis and adverse effects: five-year retrospective review

Pharmacovigilance – Clinical cases

- Deafness in a dog treated with an ear ointment containing neomycin: what is your opinion?
- Perforated duodenal ulcer and peritonitis in a dog following administration of meloxicam: what is your opinion?
- Pruritus and behavioural changes in cats after taking lotilaner: what is your opinion?
- Lack of efficacy during induced abortion: too many precautions are better than too few...
- Mortality and ear necrosis following levamisole treatment in piglets: what is your opinion?
- Ewe deaths and abortions following moxidectin treatment: what is your opinion?
- Prolonged sedation following induced vomiting in a cat: what is your opinion?
- Lack of efficacy of a vaccine against bovine respiratory disease agents in calves: what is your opinion?
- Imidocarb and tachycardia, tachypnoea, mydriasis: what is your opinion?

Antibiotics / Antimicrobial resistance

- Basis for expressing doses in International Units for certain antibiotics produced by biosynthesis (Monitoring Committee for Veterinary Medicinal Products)
- To limit environmental exposure to antibiotics in veterinary medicine treatments (Monitoring Committee for Veterinary Medicinal Products)
- Environmental contamination in a high-income country (France) by antibiotics, antibiotic-resistant bacteria, and antibiotic resistance genes: Status and possible causes
- From OIE standards to responsible and prudent use of antimicrobials: supporting stewardship for the use of antimicrobial agents in animals



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