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Post-MA surveillance of veterinary medicinal products

Annual report

October 2020 - Scientific edition

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POST-MA SURVEILLANCE OF VETERINARY MEDICINAL PRODUCTS

2019 Annual Report

A/ Introduction

Veterinary medicinal products are mainly governed by European regulations. The French Agency for Veterinary Medicinal Products (ANSES-ANMV), part of ANSES, is the competent authority for assessing and managing risks associated with veterinary medicinal products in France. Its missions are structured around three themes – assessment, authorisation and surveillance – and it carries them out as part of a wider European network. It 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, ANSES-ANMV intervenes in all stages of the veterinary medicinal product lifecycle (see Figure 1).

This entails assessing national or European marketing authorisation applications for veterinary medicinal products and taking part in the assessment of European dossiers concerning maximum residue limits (MRLs) of veterinary medicinal products in foods of animal origin. Prior to assessing applications, it can intervene as early as the drug testing phase by inspecting the laboratories implementing the trials.

It grants marketing authorisations for medicinal products, and authorises clinical trials of these products and the opening of pharmaceutical establishments (*exploitants*, wholesalers, manufacturers, exporters and/or importers of veterinary medicinal products). It also certifies exports of veterinary medicinal products.

Once a drug has been brought to market, the Agency monitors the occurrence of adverse effects resulting from its use, as well as problems of availability on the French market. It controls quality through testing, assessing reports of quality defects and verifying advertising materials on veterinary medicinal products. The Agency also monitors the operation of pharmaceutical establishments and other industrial veterinary organisations.

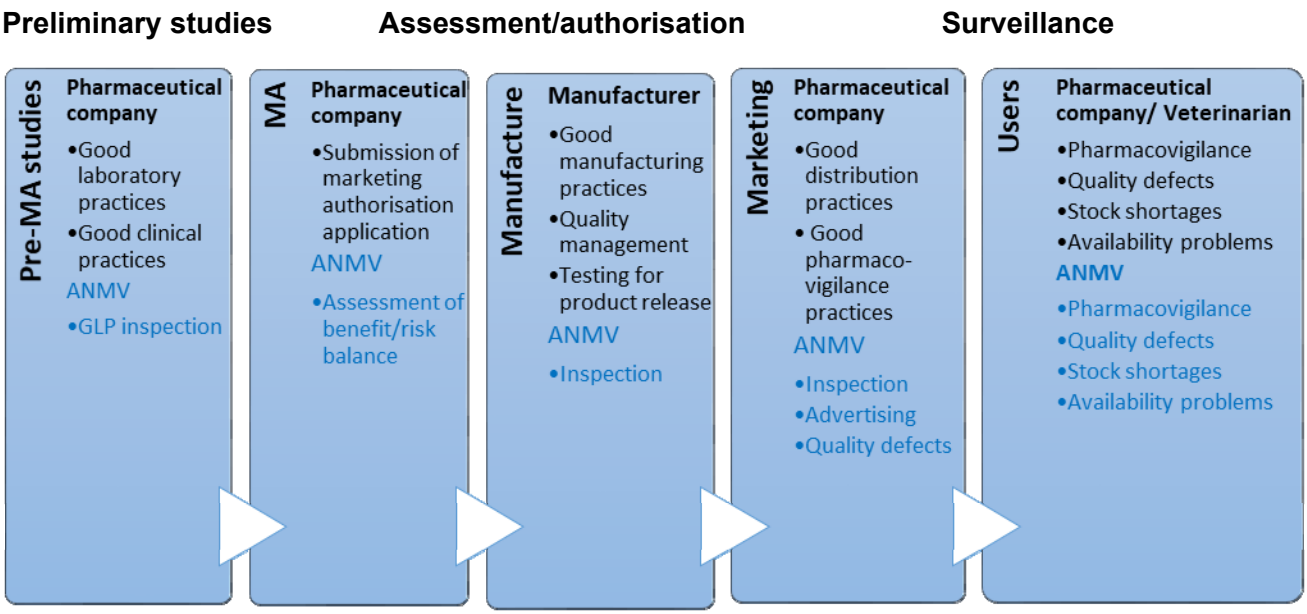

Figure 1: Role of the ANMV throughout the veterinary medicinal product lifecycle

Once the 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 drugs developed and manufactured in France (Chapter B);
- Market surveillance, which includes monitoring veterinary medicinal product quality through expert appraisals and management of quality defects, analytical control of veterinary drugs, and verification of labelling and advertising (Chapter C);
- Monitoring adverse effects through veterinary pharmacovigilance (Chapter D).

This report covers all the results related to the surveillance of medicinal products marketed in France for 2019.

B/ Inspection

As of 31 December 2019, 506 veterinary pharmaceutical establishments owned an "authorisation" for one or more activities.

In addition to these authorised establishments, ANSES-ANMV also inspects "organisations" involved in the development or manufacture of veterinary medicinal products (radiosterilisation facilities, quality control laboratories), as well as test facilities that carry out safety trials. These figures are stable compared to 2018.

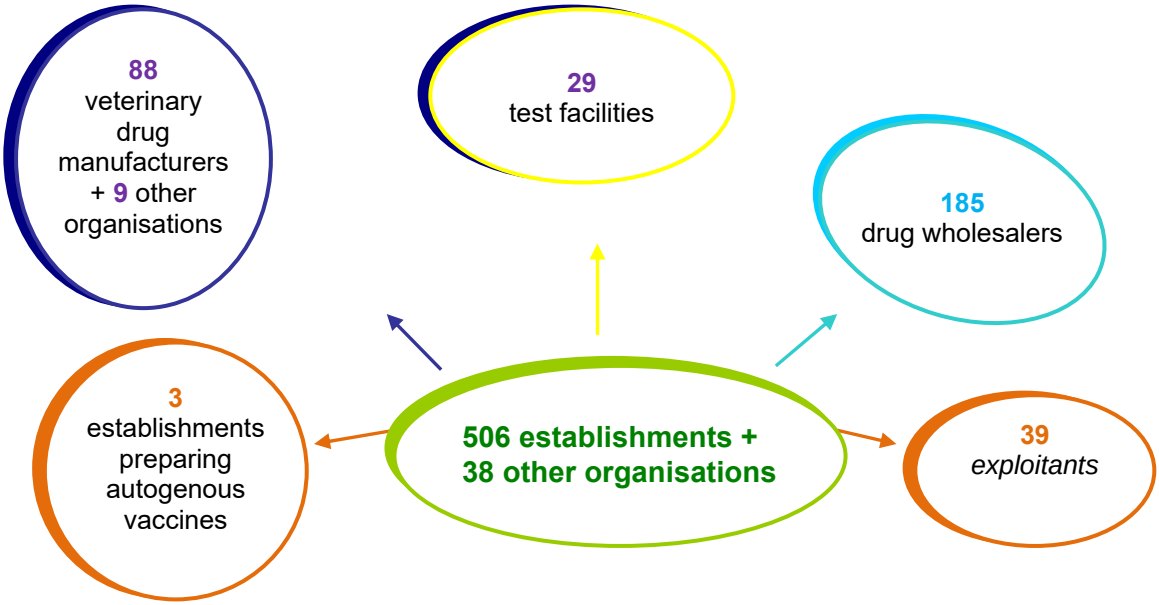

Figure 2: Breakdown of veterinary pharmaceutical establishments authorised in France and other industrial organisations inspected in 2019, according to their main activity.

To guarantee the quality, safety and efficacy of veterinary medicinal products, the surveillance scheme also relies on inspections by ANSES-ANMV of pharmaceutical establishments and other veterinary organisations to ensure compliance with the good practices inherent in their activity and enable them to maintain their certification throughout the medicinal product lifecycle.

Figure 3: Key inspection figures from 2019

The annual inspection plan is based on a risk analysis that also takes the results of previous inspections into account. This plan defines a "List 1" of priority establishments, as well as a "List 2" of lower priority establishments. Seventy-five per cent of the establishments on List 1 were inspected. The remainder were not inspected due to suspensions of activity or postponements to 2020 due to the general context (national strikes, Brexit, delays in work or commencement of activity, changes in the inspection programme of the European Medicines Agency (EMA), etc.). This then enabled 25 inspection missions on List 2 to take place. The plan also includes missions designed to meet unexpected requests for urgent health inspections or investigations: eight such inspections were carried out in 2019. Lastly, four inspections were carried out in Third Countries at the request of the EMA or French manufacturers.
This annual inspection plan ensures compliance with regulatory inspection frequencies and maintains the validity of certifications issued for veterinary pharmaceutical establishments. In 2019, 76 establishments of all categories were inspected, compared to 71 in 2018.

Figure 4: Achievements for each inspection area in 2019
(GMP: Good manufacturing practices, GDP: Good distribution practices, GLP: Good laboratory practices, GAVPP: Good autogenous vaccine preparation practices, PhV: Pharmacovigilance, EXP: *Exploitant*, FN: warning notice)

As part of veterinary drug research and development, 29 establishments are enrolled in the "Testing facility" programme. Eleven good laboratory practice (GLP) inspections, included in the annual inspection plan, were carried out in 2019. They are designed to verify that good practices are followed when carrying out laboratory trials. These trials primarily help guarantee the safety of the veterinary medicinal products tested.

Among all the establishments visited by ANSES-ANMV inspectors in 2019, a warning notice was sent to one manufacturer, but the measures implemented by this establishment were enough to rectify the situation. This establishment is now subject to heightened surveillance.

The review of 2019 inspection reports showed deviations among manufacturers mainly in the areas of 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.). For *exploitants* and wholesalers, the systems for monitoring and improving quality (mainly regarding cold chain management, handling and following up non-compliances and complaints, quality risk management) still require vigilance.

There are currently five inspectors in the inspection team, all trained veterinarians. During implementation of the inspection plan in 2019, inspectors continued being trained and accredited in the various areas where they had not yet been validated (GMP inspections for immunological products, international inspections, GLP and pharmacovigilance inspections). This supervision will continue in 2020, particularly for a recently recruited inspector, in order to meet the growing demand for both national and international inspections.

C/ Market surveillance

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

C1 – Quality defects

In 2019, of the 94 quality defects recorded, 26 resulted in drug batch recalls, mainly at the manufacturer/depositary level.
With the exception of 2015, the number of quality defects leading to batch recalls has been generally stable over the last four years.

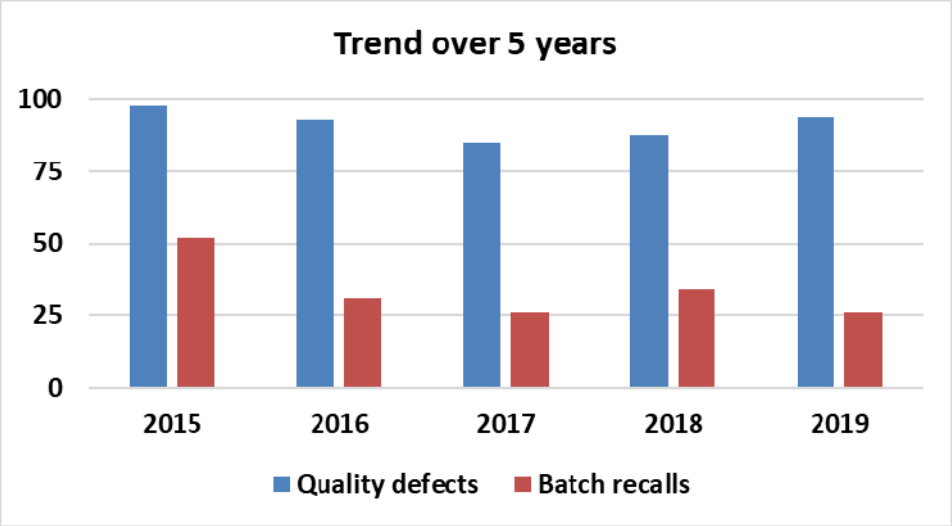

Figure 5: Trend in numbers of quality defects and batch recalls

Even though veterinarians/pharmacists can report a quality defect directly to the ANMV, almost all of these reports come from the manufacturer concerned or follow on from a change in the summary of product characteristics (SPC).

The leading cause of quality defects reported in 2019 was the level of active ingredient in stability studies (33%). Non-compliances relating to physico-chemical specifications were the second major cause of quality defects (23%). The breakdown is shown in the figure below:

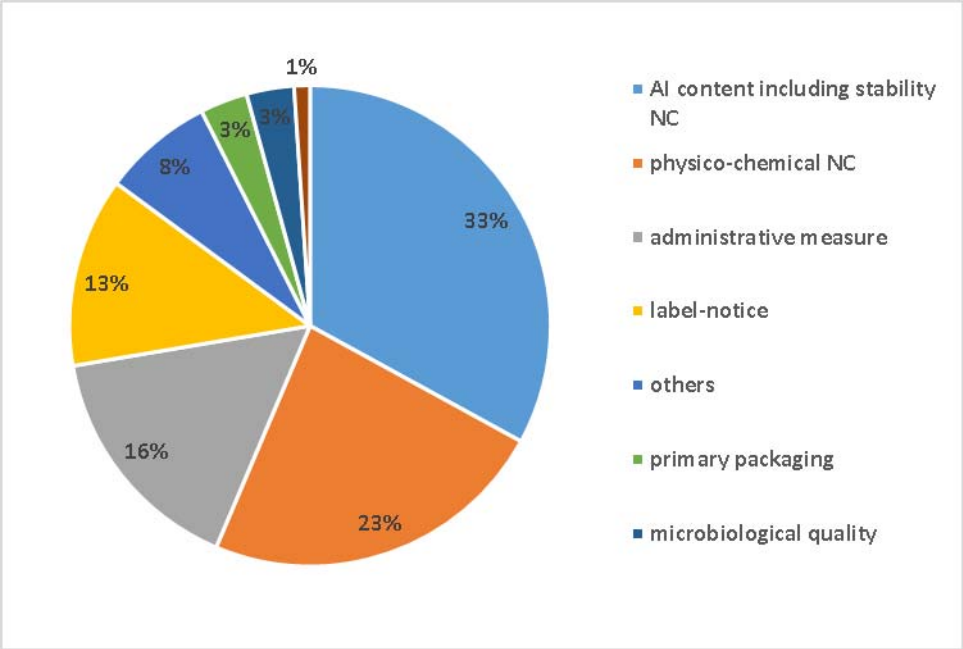

Figure 6: Breakdown of quality defects monitored in 2019 by non-compliance type (AI = active ingredient; NC = non-compliance; QD = quality defect)

Of the 26 batch recalls in 2019, 19 were at the manufacturer-depositary level, four at the wholesaler level and three at the retailer level. More than half of these batch recalls were due to a change in the SPC of the drug concerned.

C2 - Analytical quality control of veterinary medicinal products

Quality control of veterinary medicinal products involves analytical testing of drugs selected according to an annual programme based on a risk rating.

A rating grid for veterinary medicinal products is available in Europe for classifying these products in terms of their risk level. This rating grid is currently being tested for drugs with a centralised marketing authorisation (MA).
At ANSES-ANMV, the tool has been adapted to classify all veterinary medicinal products marketed in France. Six parameters were initially selected for assessing the risk level of the drug in question. The six rating criteria are as follows:

- route of administration (parenteral or ocular);
- chronic use (≥ 1 month);
- low dose or concentration (≤ 2 mg or 2%);
- complex formulation (more than one active ingredient or "emulsion" or "suspension");
- sensitive product with regard to stability (shelf life of 1 year or less or storage below 15°C);
- product intended for livestock.

In addition to these rating criteria, the programme also takes into account the results from previous years, as well as any internal requests from the ANMV. The drugs identified as most at risk are given priority by ANSES-ANMV's analytical laboratory in the annual veterinary drug control programme.

In 2019, 89 veterinary medicinal products sampled from the French market were tested, representing a total of 352 analyses. Twelve non-compliances with the MA specifications were detected, accounting for 13.5% of the drugs in the programme. These were mainly due to tablet breakability, re-suspension, and uniformity of mass for oral pastes. No non-compliance related to the concentration of active substance was identified.

The achievement rate for the annual programme was 99%.

This analytical control is carried out by the ANMV laboratory. This laboratory is also part of the European network of Official Medicines Control Laboratories (OMCL network). In 2019, it was audited by the European Directorate for the Quality of Medicines (EDQM). This audit concluded that the laboratory complies with the ISO 17025 standard and OMCL network guidelines, and confirmed the quality of the work carried out in the ANSES-ANMV laboratory.

C3 – Verification of labelling

The labelling of veterinary medicinal products sampled for the analytical control programme is also checked.
In addition to the veterinary medicinal products checked in the laboratory, 57 checks were performed following specific sampling: monitoring of minor changes to the MA, follow-up of non-compliances from 2018, and/or checks at the request of ANSES-ANMV's MA Department. The vast majority of verified labels were found to be compliant. Only three labelling non-compliances were detected when checking veterinary medicinal products analysed in the laboratory, and none on products taken from distribution sites.

These results show that the laboratories do indeed implement labelling changes within six months of notifying a change to the MA.

C4 –Advertising control

Advertising of veterinary medicinal products is regulated by the French Public Health Code (CSP)[1]. It can only relate to 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 prior declaration or authorisation. For more information, a guide to good advertising practices is available on the ANSES website.

In 2019, 528 advertising applications led to 1,171 advertising materials being verified. Of the 528 applications submitted, 110 concerned advertising requiring authorisation, and 418 advertising subject to simple declaration. This breakdown was comparable with the data from previous years, with submissions requiring authorisation accounting for between 20 and 25% of applications.

Advertisements requiring prior authorisation concerned antimicrobials, medicinal products subject to a risk management plan, medicinal products indicated for Category 1 health hazards, medicinal products containing anabolic and anticatabolic substances or β-agonists, and lastly advertisements aimed at the general public.

[1] CSP Article R. 5141-82 *et seq.*

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

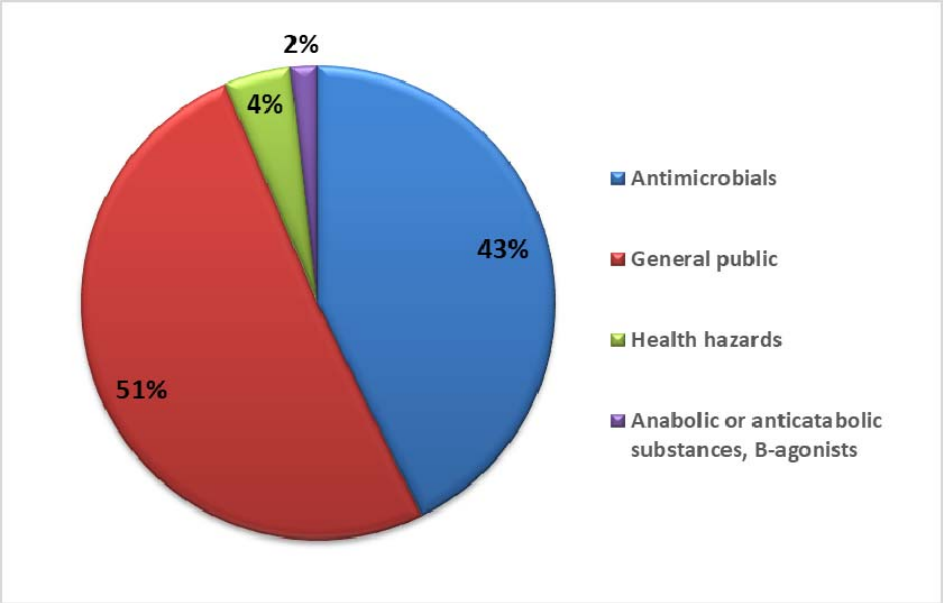

Figure 7: Breakdown of advertising applications submitted for authorisation in 2019

C5 – Classification of "borderline" products

When examining advertising dossiers or in the event of complaints filed to ANSES-ANMV, the Agency may have to classify so-called borderline products. Based on the presentations and claims made, this process seeks to determine whether or not the products in question have the legal status of veterinary medicinal products. In many cases, these products are on the boundary with biocides or feed additives. This activity has been structured within the Market Surveillance Unit, and mainly involves use of a generic assessment grid.
In 2019, ANSES-ANMV received 120 requests concerning around 585 products (a 50% increase compared with the previous year).

This included 21 notifications from professionals (manufacturers, veterinarians, etc.) and 68 from other ANSES entities or different government departments. The remaining 31 were preliminary requests from companies for regulatory opinions (before their products were placed on the market, imported or exported, for example).

Following these notifications, in most cases, a simple reminder of the regulations in force was sufficient for the companies to bring the products into compliance (removal of the product from the promotional material, changes to product claims, etc.). Nevertheless, in 2019, nine letters of formal notice were written, concerning one or more products.

These letters were mainly on two topics. The first has been a sensitive issue for the classification activity since 2016: the different medicinal products without MAs that are proposed for bees. The second was a new issue: products containing cannabidiol. In this context, ANSES-ANMV published a brief reminder on its website of the ban on the use of cannabis and its derivatives for therapeutic purposes in veterinary medicine.

In 2019, there were no reports of any suspension of marketing authorisation for products classified as medicinal products, by presentation or function.

Lastly, a position paper on the legal classification of borderline products was published on the ANSES website in May 2019 (https://www.anses.fr/fr/system/files/ANMV-notedepositionqualificationdesproduitsfronti%c3%a8res.pdf).

C6 – Management of stock shortages – availability of veterinary medicinal products

Just like quality defects, stock shortages must be reported to ANSES-ANMV by the companies marketing the products. 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 shared. In 2019, 68 cases of shortages were reported. The breakdown by drug type is shown in the figure below:

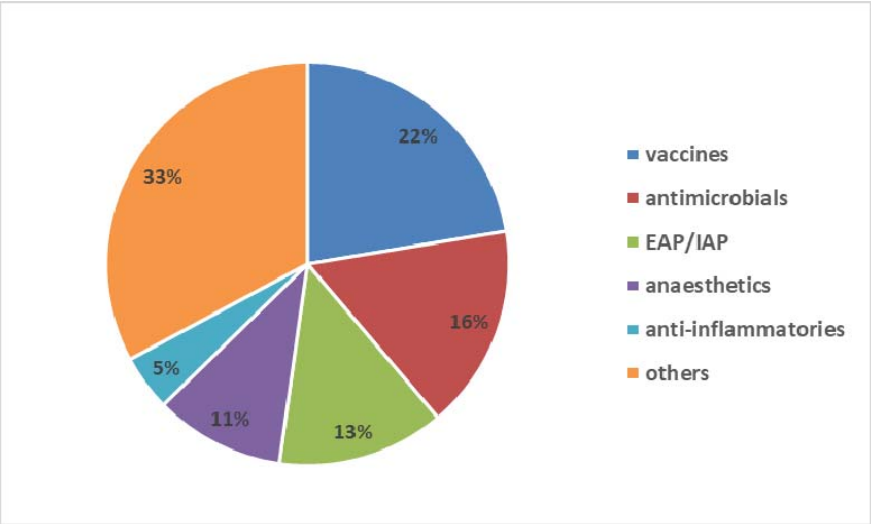

Figure 8: Breakdown of stock shortages by type of drug in 2019
(EAP = external antiparasitic; IAP = internal antiparasitic)

This breakdown is similar to that of previous years: reports of shortages mainly concern vaccines (nearly 40%), with the cattle-sheep-goat (33%) and poultry-lamb (27%) sectors remaining the most affected by these shortages.

Of the critical stock shortages in 2019 (22 drugs), ANSES-ANMV implemented solutions in half of the cases:

- Authorisation to import a medicinal product that has not been authorised in France;
- Exceptional batch release;
- Extending batch shelf life.

A stock shortage is deemed to be critical when it is liable to induce a risk to human health, animal health and welfare. Since May 2019, critical supply shortages have been published on the ANSES-ANMV website. This information is available from the supply shortages page, which includes a summary table of current critical supply shortages. Additional information for each drug is available via a link in the table. This measure was introduced as part of the good practices for managing supply shortages of veterinary medicinal products, published online in late 2018.

The ANSES-ANMV Market Surveillance Unit takes part in EMA working groups on "Shortages" and "Availability". In July 2019, their work led to the publication on the EMA website of guidance for

marketing authorisation holders to facilitate reporting of these shortages. At the same time, the work of the EMA/HMA Task Force on the availability of human and veterinary medicinal products led to the establishment of the single point of contact (SPOC) network in the agencies of European Union Member States, whose aim is to facilitate information and coordination between the various authorities. For more information, the EMA has published various online documents on this theme (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines)

D/ Pharmacovigilance

- D1 – 2019 review

- Trend in total numbers of reports of adverse effects

In 2019, 4,605 pharmacovigilance reports were notified to ANSES-ANMV, representing a 3% decrease in the total number of reports compared to 2018 (Figure 9). These data correspond to the number of reports of adverse effects occurring in animals or humans following administration of/contact with a veterinary medicinal product or, in the framework of the "cascade" approach, adverse effects occurring in animals following administration of a medicinal product designed for human use.

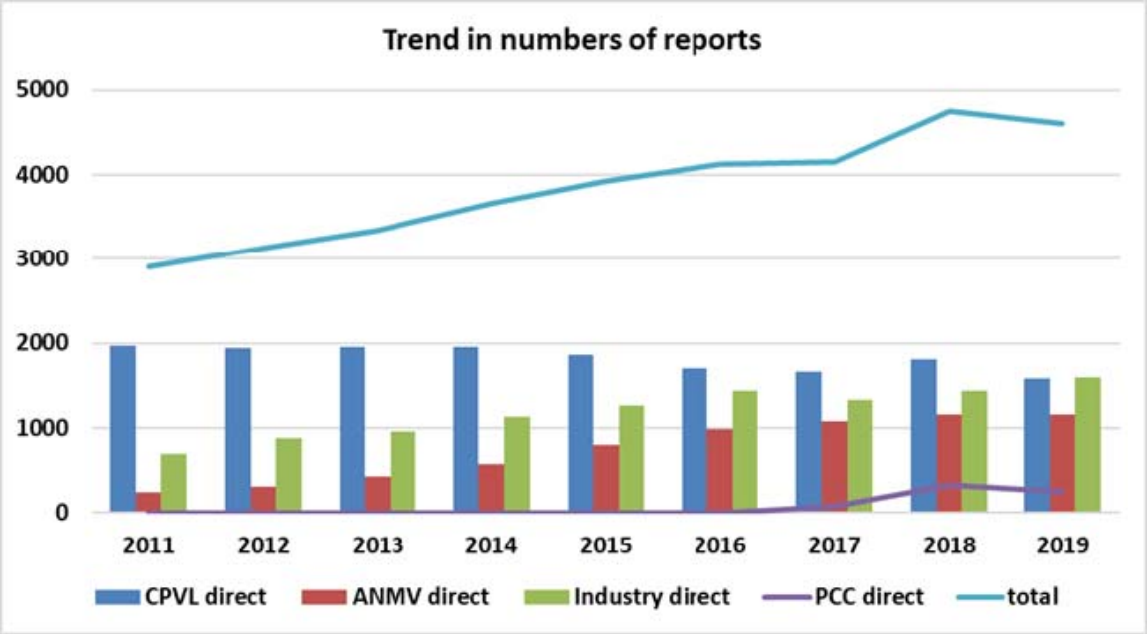

Figure 9: Trend in numbers of reports from 2011 to 2019 according to reporting channels
ANMV direct: reported via the online submission site; CPVL direct: reported to the CPVL by post/email or telephone; industry direct: reported to the MA holder; PCC direct: human cases reported to poison control centres.

Part of the decrease in the total number observed in 2019 was due to a temporary interruption in the transmission of human cases from human poison control centres (PCCs) in the last few months of 2019. This interruption, due to a change in IT tools, resulted in a 20% fall in the number of human cases compared to 2018.

In animals, the total number of cases also decreased very slightly compared to 2018 (-1.5%). However, this result varies according to the reporting channel chosen by the initial reporter: the number of reports sent by industry increased slightly, the number of reports submitted online remained stable, and the number of reports transmitted via the Veterinary Pharmacovigilance Centre in Lyon (CPVL) decreased.

Typology of reports	
Adverse effects in animals	3,589 (77.9 %)
Lack of efficacy	697 (15.1 %)
Residue issues	5 (0.1 %)
Environmental issues	0 (0.0 %)
Adverse effects in humans	314 (6.8 %)
Total	4,605 (100%)

Figure 10: Typology of reports in 2019

Although the typology of reports remained broadly similar to that observed in previous years, with the vast majority of reports concerning adverse effects in the strict sense of the term in animals (78% of the total number), the 2019 results confirm a trend already identified in recent years, namely that the number of reports of suspected lack of efficacy continues to increase (15% in 2019 compared to 8-10% in previous years).
The graph below shows the growth in numbers of reports of suspected lack of efficacy. Between 2011 and 2019, this number increased by 83%, and this trend has become more pronounced since 2017. In comparison, the number of reports of adverse effects in the strict sense of the term in animals increased by 31% between 2011 and 2019.

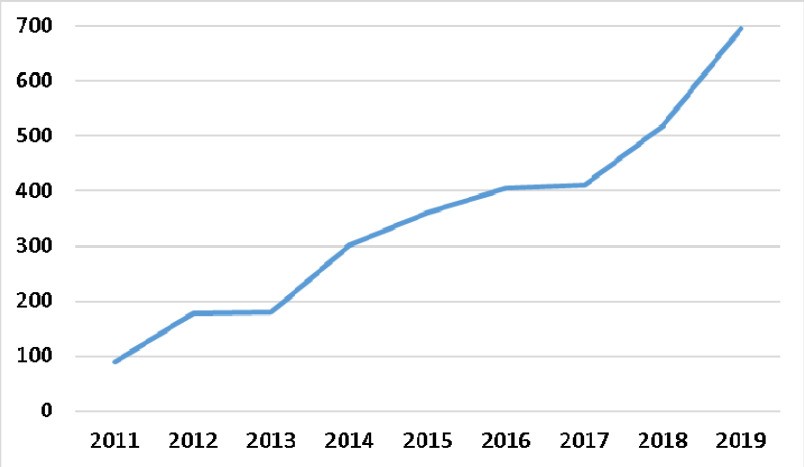

Figure 11: Trend in numbers of reports of suspected lack of efficacy

This increase concerns most species. For the three main species, which were dogs, cattle and cats, respectively 230, 170 and 105 cases of suspected lack of efficacy were recorded in 2019. The vast majority of these reports were for vaccines (68%) and antiparasitic agents (23%).

This increase in reports probably testifies to greater awareness among veterinarians and breeders of this component of pharmacovigilance, as a result of the training and communication measures implemented in recent years.
For example, the adverse effects of vaccines (including suspicions of lack of efficacy) have been covered in specific studies published in professional veterinary journals (see Section D2 below).

- Reports by species and therapeutic category

Since a single report may concern several medicinal products, a total of 5,543 drugs were involved in the 4,605 reports.
As shown in the graph below, domestic carnivores were yet again involved in more than 80% of all reports concerning animals.

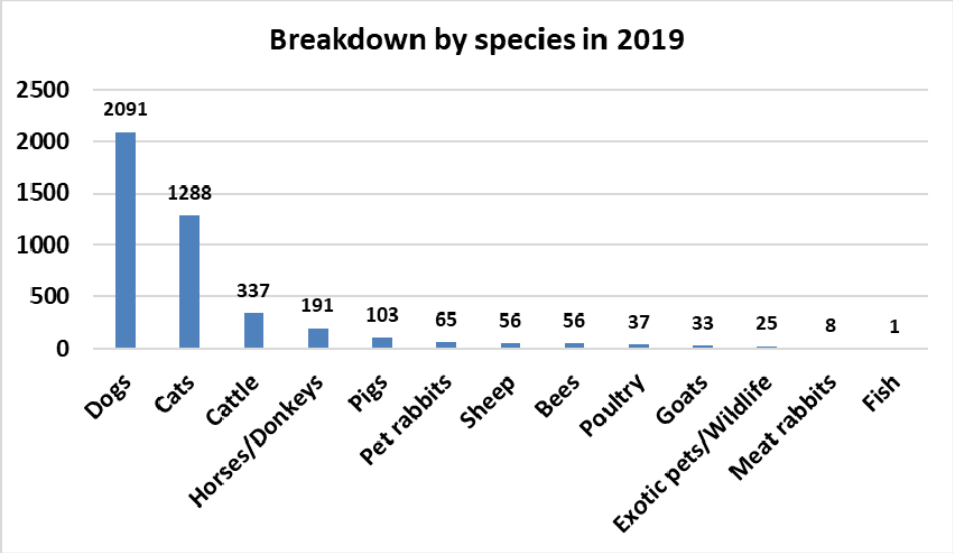

Figure 12: Breakdown by species in 2019

Vaccines remained the main products implicated in an adverse event in most species, except for cats and bees, for which external antiparasitics were the most frequently cited.

The figure below shows the breakdown of reports by therapeutic category. In order to improve its legibility, only those therapeutic categories cited in more than 2% of reports are included. All the therapeutic categories by species are shown in Figure 14.

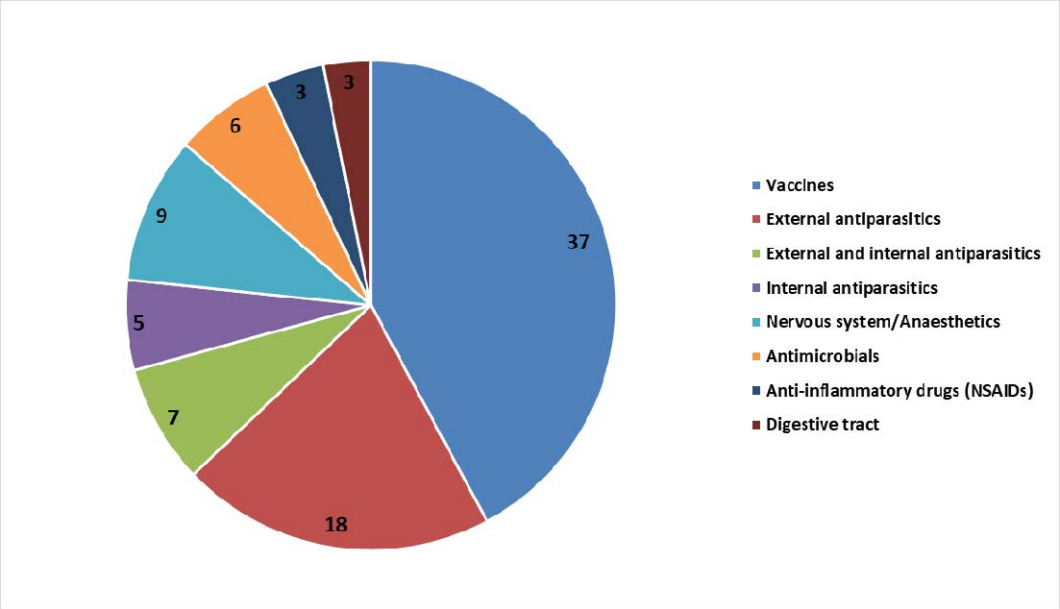

Figure 13: Overall breakdown in percentage of reports for the most frequently cited therapeutic categories (>2%)

Figure 14: Breakdown by therapeutic category of the number of reports according to species in 2019

	Dogs	Cats	Cattle	Horses/ Donkeys	Pigs	Pet rabbits	Sheep	Bees	Poultry	Goats	Meat rabbits	Fish	Exotic pets/Wildlife	General total
Vaccines	1076	341	232	158	129	48	25	0	40	11	8	1	3	2072
External antiparasitics	523	409	9	4	1	10	0	56	0	1	0	0	5	1018
External and internal antiparasitics	110	205	22	12	0	6	18	0	0	12	0	0	1	386
Internal antiparasitics	141	97	24	4	7	0	9	0	1	7	0	0	2	292
Nervous system/Anaesthetics	258	161	19	19	1	9	4	0	0	0	0	0	7	478
Antimicrobials	144	89	55	18	4	2	0	0	6	4	0	0	3	325
Anti-inflammatory drugs (NSAIDs)	120	42	11	11	3	1	0	0	0	0	0	0	2	190
Digestive tract	80	40	29	1	0	1	2	0	0	0	0	0	1	154
Cardiovascular and circulatory system	51	31	2	2	0	0	0	0	0	0	0	0	0	86
Hormones	81	45	1	3	0	1	0	0	0	2	0	0	3	136
Genital and reproductive organs	80	17	9	2	0	0	9	0	0	0	0	0	1	118
Ocular and auricular products	44	31	0	1	0	0	0	0	0	0	0	0	0	76
Dermatology	82	25	0	0	0	2	0	0	0	0	0	0	0	109
ntineoplastic and immunomodulator agent	14	14	1	0	0	0	0	0	0	0	0	0	0	29
Blood and blood-forming organs	4	3	7	0	0	0	0	0	0	0	0	0	0	14
Respiratory system	7	0	1	0	0	0	0	0	0	0	0	0	0	8
Other	32	20	0	0	0	0	0	0	0	0	0	0	0	52
General total	**2847**	**1570**	**422**	**235**	**145**	**80**	**67**	**56**	**47**	**37**	**8**	**1**	**28**	**5543**

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

- MA amendments

The pharmacovigilance reports and their analysis, at either national or European level, enable the summaries of product characteristics (SPCs) to be amended to take account of the new information obtained. These amendments concerned 77 drugs in 2019, compared to 71 in 2018. This assessment of the pharmacovigilance data mainly led to the "Adverse events" section of the SPCs being supplemented, with the addition of new clinical signs or changes to their incidence of occurrence, but also enabled new warnings/contraindications and precautions for use to be added.

These changes are made public via ANSES-ANMV's "Monthly newsletter on veterinary medicinal products" published on the ANSES website.

D2 – Signal detection

The purpose of pharmacovigilance is to detect any new signal as quickly as possible – whether it is an unexpected adverse event, or one that is expected but whose frequency or severity is unexpected – and then to take appropriate management measures. These measures can range from an amendment to the summary of product characteristics (addition of a precaution for use, change to the "Adverse events" section, etc.) to withdrawal of the marketing authorisation, or a communication to alert veterinarians and/or owners/breeders.

Signal detection facilitates the early identification of potential safety problems (adverse events, product interactions, etc.) by highlighting "higher than expected" frequencies of drug-event associations without exposure data.

It is carried out via several complementary approaches:

- Observational surveillance carried out when assessing each report;
- A trend analysis that compares reported data from different time periods;
- Calculation of statistical indicators.

The first two approaches, traditionally used by ANSES-ANMV, have been supplemented by the implementation of signal detection based on the proportional reporting ratio (PRR) statistical method. This method compares the proportion of an effect (clinical sign/syndrome) due to a drug to the proportion of the same effect but from all the other drugs in the database, in a 2x2 contingency table (method of representing data from a count to estimate the dependence between two characters), stratified by species.

This method is highly sensitive and generates many false positives. It is also highly dependent on the number of reports recorded and the quality of the data. Consequently, the signals detected statistically must then undergo individual clinical analysis before they can be validated.

This untargeted signal detection is carried out every two months and is applied to the reports registered in France by ANSES-ANMV over the study period. It supplements the current analysis system and has already enabled the identification of signals that have resulted in changes to the SPCs.

D3 – Work carried out in communication on veterinary pharmacovigilance

ANSES-ANMV regularly communicates on different themes to promote pharmacovigilance. Topics include a summary of the reports recorded, related to a specific drug, therapeutic category and/or species, as well as position papers on ways to facilitate reporting and improve report quality.

This information is disseminated via different media, such as the ANSES website, the newsletter of the French Veterinary Association National Council, the trade press, and congresses. In addition, ANSES-ANMV promotes research and thesis work in the field of veterinary pharmacovigilance by providing access to the data in the national pharmacovigilance database.

Articles published on pharmacovigilance in 2019 included a feature on drug-induced nephrotoxicity in domestic carnivores (*Le Point Vétérinaire* – June 2019):

- Retrospective study of pharmacovigilance cases reported in dogs and cats: drug nephrotoxicity
- Prevention and management of renal adverse effects in dogs and cats.

A reminder of the precautions to be taken when using altrenogest medications was also published on the ANSES website (https://www.anses.fr/en/content/regumate-equine-veterinary-medicinal-product-horses-should-be-used-caution) and then published in specialist journals in the equine and pig sectors.

Monthly publication of clinical cases

The monthly publication in *La Dépêche Vétérinaire* of studies of individual cases of adverse events reported to ANSES-ANMV, which began in mid-2018, continued throughout 2019.

Its aim is to improve understanding of the analytical work carried out on each report by the veterinary experts of ANSES-ANMV and the CPVL.

Clinical cases are selected for their potential interest to the veterinary profession. The description of each clinical case is followed by the pharmacovigilance specialist's analysis of the possible relationship between the administered drug(s) and the clinical sign(s) observed subsequently, as well as the resulting causality score.

Publication of reviews on adverse effects of vaccines

Adverse effects of vaccines (including suspicions of lack of efficacy) in dogs and horses were addressed in specific studies in 2019, published in professional veterinary journals. A review of the adverse effects of vaccines in cats was the subject of a veterinary thesis. Complete features on vaccination were therefore published respectively on cats in the journal *Le Point Vétérinaire* (March 2020) and on horses in the journal *Pratique Vétérinaire Equine* (April 2020). Each one included an analysis of the adverse effects recorded by ANSES-ANMV, good practice recommendations and a review of the available vaccines.

Direct communication with livestock farmers

Although veterinarians are the priority target for ANSES-ANMV when promoting pharmacovigilance, since they generate more than 90% of reports, pharmacovigilance data are also used to raise awareness among farmers about the importance of proper drug use. For example, articles based on individual cases of adverse effects in sheep or goats reminded farmers in these sectors of the importance of good injection practices[2].

[2] *Mieux utiliser les médicaments avec la pharmacovigilance* [Better use of drugs with pharmacovigilance] - *Réussir Pâtre* Issue 664 – May 2019 and *Réussir La Chèvre* Issue 352 – May/June 2019

Initiatives to promote pharmacovigilance are not limited to the publication of individual articles. ANSES-ANMV regularly attends various professional congresses such as the national meetings of the veterinary technical groups (GTVs) and the annual congresses of the French Association of Veterinarians for Pets (AFVAC) and the French Equine Veterinary Association (AVEF).

In October 2019, ANSES-ANMV organised its second one-day meeting with 100 people representing all its stakeholders in the veterinary medicinal product supply chain: veterinary pharmaceutical manufacturers, wholesalers, veterinarians, livestock farmers and World Organisation for Animal Health (OIE) representatives. One of the day's workshops was specifically devoted to pharmacovigilance: "Twenty years of pharmacovigilance: what expectations and outlook for veterinary pharmacovigilance?" This lively workshop was an opportunity for each stakeholder to discuss and identify areas of work that will be included in ANSES-ANMV's work programme, a particular objective being to improve the visibility of the communication measures implemented.

Lastly, the EMA has made available to the public a certain amount of information on adverse events concerning veterinary drugs registered in the European Eudravigilance database (http://www.adrreports.eu/vet/en/index.html). The data are published without taking into account any possible causal link between a medicinal product and the clinical sign(s) observed or the number of animals exposed, and cannot therefore be used to conclude as to any risk associated with a particular medicinal product.

Searches can currently be carried out based on the name of a medicinal product or active substance for centralised MAs, and on an active substance only for national MAs. Statistics on geographical distribution, species, breed and type of effect, as well as the individual data of the reports in question, are thus accessible to the public.

E/ Outlook for 2020

The European regulation on veterinary medicinal products provides for numerous delegated and implementing acts. In order to prepare these secondary acts, the European Commission mandated the EMA to provide scientific and technical opinions. ANSES-ANMV experts have been heavily involved in the groups working on this, notably by holding several chairs and co-chairs. Their work will be carried out on a tight schedule with, in particular, opinions on pharmacovigilance finalised by May 2020 and opinions on good distribution practices (both finished products and active ingredients) by June 2020.
At the same time, ANSES-ANMV is also involved in work on the IT tools to be developed, whether for the veterinary medicinal products database or the revision of the pharmacovigilance database.

Also at European level, ANSES-ANMV is fully involved in pursuing the implementation of the mutual recognition agreement (MRA) between the European Union and the United States for the inspection of manufacturing sites for chemical veterinary medicinal products (excluding external antiparasitics) on their respective territories.

F/ CONCLUSION

Under post-MA surveillance activities, 76 inspections in establishments were carried out by ANSES-ANMV, representing nearly 700 inspection days. Reports of quality defects, which have remained generally stable in recent years, led to batch recalls in 25% of cases, while analytical controls of medicinal products found a 13% rate of non-compliance. Stock shortages primarily concerned antimicrobials and vaccines, affecting mainly the cattle, sheep and goat sectors, as well as the poultry sector. ANSES-ANMV is closely involved in managing these disruptions and identifying alternatives to critical medicines. Since 2019, information on these critical supply shortages has been available on the Agency's website. In terms of pharmacovigilance, the annual increase in the number of reports seen since 2011 did not continue in 2019, mainly due to an artefact (unforeseen event). However, reports of suspected lack of efficacy increased by 83% between 2011 and 2019. The Agency is continuing its communication campaigns targeting professionals, in order to promote veterinary medicinal product pharmacovigilance.

2019 figures for post-MA activities

675 inspection days - 76 organisations inspected

94 reports of quality defects

26 batch recalls

89 analytical controls of drugs

68 stock shortages reported, including 22 critical

1,171 advertising materials submitted

120 requests for classification (585 products)

4,605 adverse effect reports

In addition, in order to meet the new challenges facing the Agency and rebalance the different specialist departments, ANSES-ANMV undertook a reorganisation of its structure around three "specialist" departments and three units:

- A Scientific Assessment Department, an Administrative Decisions Department and an Inspection, Surveillance & Pharmacovigilance Department;
- A European & International Affairs Unit, a Legal Affairs & Litigation Unit and an Antimicrobial Resistance Unit.

This new organisation will show more clearly the separation of risk assessment from risk management, as is the case for other regulated products at ANSES, and will enable all responsibilities regarding post-MA surveillance of medicinal products to be grouped together within the same department.

The main expectations for 2020 in the monitoring of veterinary medicinal products are fully in line with ANSES-ANMV's general activity programme and primarily concern two topics.

The first relates to the Agency's European positioning with, as mentioned in the previous section, the work to be carried out as part of the revision of European legislation in the field of veterinary medicinal products.

The second priority concerns communication, which is key to the success and recognition of the work of ANSES-ANMV. In this context, ANSES-ANMV's actions are structured around several themes: maintaining the number of publications in specialised journals, improving the information available on the website, and ensuring a greater and more visible presence for ANSES-ANMV at congresses, exhibitions and seminars.

This fifth annual report on activities relating to post-MA surveillance of medicinal products shows that the quantitative results of this activity are fairly consistent from one year to the next. These surveillance activities, carried out by the ANMV throughout the medicinal product lifecycle, help to improve the safety of veterinary medicinal products

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