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Veterinary pharmacy – a major challenge for sustainable livestock production

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■ **Veterinary pharmacy is an important part of farm animal health and welfare management. The correct use of drugs remains essential for more sustainable livestock production. A good understanding of the regulatory environment, industry needs and future challenges is essential to meet these new requirements.**

Introduction

Veterinary pharmacy is an important issue in animal husbandry. Therapeutic practices are gradually changing. For example, the use of antimicrobials (antibiotics, antiparasitics) is now less systematic and better reasoned, while the use of analgesics is becoming more widespread. One of the difficulties for the breeder is the multiplicity of people involved, resulting in more or less contradictory advice. The veterinarian, with his specific skills, must remain the privileged partner, the equivalent of the "family doctor", as the conductor of the herd's health. Sometimes, for various reasons (cost, availability, etc.), this role slips through their fingers. However, for any treatment, whatever its nature, it is the veterinarian who is best placed to assess the risk/benefit balance not only for the animals, but also for humans and the environment.

The aim of this paper is to present veterinary medicines for production animals, their role and the issues at stake in a complex regulatory, scientific, economic and societal environment in France. To this end, it is divided into three parts. The first part presents the regulatory characteristics of veterinary medicines. The second part describes the main uses of veterinary drugs in France today in order to understand the needs of the various sectors. The final part focuses on the main issues for the future of veterinary medicines, highlighting the main problems that the livestock sector will have to overcome: a deteriorating image in the public eye, the fight against antimicrobial resistance, animal welfare, ecotoxicity and the impact of treatments on biodiversity, and compliance with charter and labelling requirements. In France, as in Europe, livestock farming is more than ever at a crossroads, forcing it to reinvent itself.

1. Veterinary medicines: very strict regulations for a product like no other

When we talk about veterinary pharmaceuticals, we first think of medicines used in animal husbandry (e.g. antibiotics, antiparasitics, vaccines or anti-inflammatories). However, in a broader sense, some biocides (e.g. hygienic products for teat antisepsis in dairy farming, insecticides for fly control in buildings or products for rodent control), some feed additives (e.g. mineral and vitamin supplements for animal feed, preservatives for silage or coccidiostats for poultry feed) and some so-called alternative products (plant extracts or essential oils) could also be included in animal pharmacy. We will confine ourselves here to a presentation of veterinary medicines, but in the boxes, the reader will find information on the other categories of products used, such as biocides (Box 1), additives (Box 2), or complementary and alternative practices (Box 3).

A new European regulation (2019/6 on veterinary medicinal products (125 pages) and a new European regulation (2019/4) on medicated feedingstuffs and intermediates (22 pages) will apply from 28 January 2022 without transposition into national law. This presentation is therefore based solely on these new European regulations.

■ 1.1. Definitions

A medicinal product is any substance or combination of substances which meets at least one of the following conditions:

Box 1. ***What is a biocide?***

Biocidal products are products designed to destroy, render harmless or repel harmful organisms. By definition, they are active products and can therefore have adverse effects on humans, animals or the environment. European Regulation 528/2012 on the making available on the market and use of biocidal products came into force on 1 September 2013. It aims to ensure that effective biocidal products are available on the market and that the risks associated with their use are controlled. The implementation of the legislation is divided into two stages: i) an evaluation of biocidal active substances leading to their approval or their rejection, then ii) an evaluation of products containing them in order to obtain a marketing authorisation (MA). The Ministry of Ecology, Sustainable Development and Energy is the competent authority for biocidal products in France and issues marketing authorisations for biocidal products.

There are 22 types of biocidal products (TP) divided into 4 groups: disinfectants, protective products (preservatives, wood preservatives), pesticides and others. Biocidal products include disinfectants with antimicrobial activity for surface disinfection (TP2), antiseptics for use on the skin or mucous membranes of animals (TP3), rodenticides (TP14), but also insecticides or acaricides to control infestations of various arthropods such as flies or red lice (TP18). There is therefore sometimes a fine line between a biocide and a medicinal product. For example, a product containing permethrin for the control of fly infestations, which is applied directly to the back of cattle, was marketed as a biocide. Considering that it was a veterinary antiparasitic, Anses (the French National Agency for Food, Environmental and Occupational Health and Safety) decided in 2016 to suspend the marketing of this product. The administrative court of Nîmes overturned this suspension in 2019. The Administrative Court of Appeal of Marseille reinstated the suspension in 2021. It considered that if the product meets the definition of a biocide and as such can be marketed on a large scale without any real control of its use, it also meets the definition of a veterinary medicinal product in terms of its function and presentation and is also likely to present a risk to animal and human health. This product must therefore be considered a veterinary medicinal product and be subject to these rules. However, the legal process to reach this decision has been long.

Biocidal products are available over the counter, but some are banned from sale to non-professional users (e.g. those for which resistance is suspected or proven). The requirements for the manufacture, quality, risk assessment and distribution of biocidal products are less stringent than those for pharmaceuticals, although these requirements have increased significantly in recent years and controls are more frequent.

(a) it is presented as having curative or preventive properties in respect of animal disease; or

(b) it is intended to be used in or administered to animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological; or metabolic action; or

(c) it is intended to be used in animals for the purpose of making a medical diagnosis; or

(d) it is intended to be used for the 'euthanasia of animals'.

In analysing this regulatory definition, a distinction is therefore made between medicinal products by presentation or by function:

– **Presentational medicinal products** (a): these are "substances or compositions presented as having curative or preventive properties". For example, a preparation may be presented as "treatment of clinical mastitis caused by staphylococci and streptococci" and therefore be classified as a medicinal product by presentation. Note that this presentation may be explicit (as in the example above) or implicit (e.g. a particular dosage form such as an injectable solution).

– **Functional medicinal products** (b): These are "substances or compositions which restore, correct or modify biological functions". For example, it could be a substance with an anti-inflammatory pharmacological action. This second category considerably broadens the scope of qualification, which could even be extended to food! The limit is set by the administration: only what is administered with a therapeutic intention, even if this is not explicitly stated, is considered a medicinal product.

A distinction is made between:

– **Pharmaceutical specialities**, i.e. any medicine prepared in advance, presented in a specific packaging and identified by a specific name (Article L.5111-2 of the French public health code). This is the classical form that one thinks of when talking about medicines, the one that is normally available in pharmacies.

– **Veterinary autovaccines** are, in simple terms, inactivated immunological veterinary medicinal products obtained from pathogens or antigens from one or more animals belonging to the farm in question. To date, these medicines have mainly been used in monogastric or fish farming. Only three laboratories in France are currently authorised to produce them.

– **Magistral preparations** are extemporaneous preparations made according to a veterinary prescription by an authorised person and intended for one or more animals of the same farm. These preparations can be made from raw materials for pharmaceutical use, and also from plant extracts or essential oils.

■ 1.2. Marketing authorisation (MA)

Any pharmaceutical product can only be marketed after a favourable decision has been made by a competent authority: this is known as the marketing authorisation or MA. This decision is based on a prior assessment of the quality, safety and efficacy of the product. The MA may be granted following a national procedure (via the ANMV – National Agency for Veterinary Medicines) or, more generally, a Community procedure (via

Box 2. ***What is an additive?***

Feed additives are products used in animal nutrition because of their effects on the feed itself, on animals, on food obtained from animals that have consumed the additive, or on the environment. For example, additives are used to improve the palatability of feed, to meet nutritional requirements or to improve the performance of healthy animals.

Additives used in animal feed can include:

– technological additives (preservatives, antioxidants, emulsifiers, acidity regulators or silage additives, etc.),

– sensory additives (flavourings, colourings, etc.),

– nutritional additives (vitamins, amino acids and trace elements),

– zootechnical additives (digestibility enhancers, etc.),

– coccidiostats (antiparasitic agents).

Feed additives can only be placed on the market if they have been authorised following a scientific evaluation by the European Food Safety Authority (EFSA) which demonstrates that the additive does not have an adverse effect on human and animal health or the environment.

the CVMP – Committee for Medicinal Products for Veterinary Use). However, for certain homeopathic medicinal products, in the absence of a specific therapeutic indication, a simple registration may be sufficient.

The dossier required to obtain a marketing authorisation is highly regulated. It consists of several administrative, technical and scientific elements, divided into four parts according to the Community format:

– Part I, called **Overall summary**. It contains the **Summary of Product Characteristics(SPC)**. It presents the pharmaceutical, pharmacological, toxicological and therapeutic characteristics of the medicinal product as validated and authorised by the competent authority. It is used as a guide to the correct use of the medicinal product and as a legal reference for defining the responsibilities of the prescriber, dispenser and user with regard to the conditions of use. It also contains the information that must appear on the labelling, package leaflet and in advertising.

– Part II, entitled **Quality Aspects**. It includes, in particular, the qualitative and quantitative composition of the constituents of the medicinal product, information concerning its pharmaceutical and galenical development, a description of the method and conditions of manufacture, a description of the techniques used to control the raw materials and the finished product, and the protocols and results of the stability tests justifying the stability period stated for the medicinal product.

– Part III: **Safety and residues assessment**. It contains a large amount of toxicological information enabling the risk to be assessed, for the target species, the human user (e.g. the breeder or the veterinarian) and the environment (ecotoxicology). It also includes studies on the depletion of residues in food of animal origin (milk, muscle, liver, kidney, etc.), which are essential for determining a withdrawal period (see next section).

– Part IV, called **clinical assessment**. It includes the results of pre-clinical studies and clinical studies carried out in the laboratory and in the field.

The marketing authorisation (MA) is therefore based on a rigorous assessment of the **quality**, **benefits (efficacy)** and **risks (safety)** of the medicine by an independent authority.

The marketing authorisation is only granted if the risk-benefit ratio is deemed to be favourable, particularly in relation to the disease being treated, and existing therapies. It guarantees the user a very high level of knowledge about the medicine in question. It is accompanied by post-authorisation monitoring (pharmacovigilance) to complete the safety (and even efficacy) data for animals, humans and the environment.

■ 1.3. Residues and withdrawal period

Any veterinary medicinal product administered to livestock is likely to persist as a residue, whether or not in a modified form, in foodstuffs of animal origin (muscle, liver, kidney, fat, hide, milk, eggs and honey). Residues thus consist of all pharmacologically active substances, including excipients and degradation products of substances present in the medicinal product. The assessment of the risk associated with the presence of residues in foodstuffs intended for human consumption leads to the establishment of Maximum Residue Limits (MRLs) for each active substance (active ingredient or, more rarely, other components of the formulation). The MRL is the maximum level of residue in or on food that the EU can accept as legally admissible or that is recognised as posing no risk to the consumer. Their setting is highly regulated and based on numerous toxicological studies. Therefore, in order to be authorised for use in farm animals, a medicinal product may only contain pharmacologically active substances whose MRLs have been evaluated and are listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009.

Once MRLs have been set, it is necessary to ensure that food does not contain residues at concentrations exceeding the MRLs. This is done by setting a withdrawal period (WP). This is the time that must elapse between the last administration of a veterinary medicinal product and the slaughter or production of food from that animal. At the end of this period, the concentrations of pharmacologically active substances in the various tissues consumed by humans (including meat, offal, milk, eggs and honey) are all below the MRLs, which means that these foods are once again safe to be consumed by humans.

Box 3. ***Complementary and alternative treatments***

Complementary practices refer to non-traditional practices used in conjunction with conventional medicine, while alternative practices refer to non-traditional practices used instead of conventional medicine. These practices are based on the best available evidence, even if this evidence does not meet the strictest criteria for efficacy and safety. An example is the use of products based on plants or plant extracts, essential oils, etc. Depending on the choice made by the manufacturer at the time of placing on the market, these products may be marketed as medicines, biocides or additives, each meeting specific regulatory requirements. In most cases, however, these products do not comply with any of these regulations, and this does not prevent them from being marketed!

Unless they have the status of a medicine, biocide or additive, these products raise a number of issues in 2022:

– on quality: their production is not subject to any binding specifications or external control system. Verification of the content of impurities or pollutants depends solely on the good will of the producer. By definition, especially in phytotherapy, the composition of the product varies according to the raw material (plant), which makes it impossible to guarantee the repeatability of treatments.

– on safety: in animal production, one of the issues is food safety for the consumer of animal products. For example, an essential oil, a lipophilic substance applied to the udder of a lactating cow, will inevitably be found in the animal's milk. However, the withdrawal time applied will generally be zero. Contrary to what is required for medicinal products, no study is required on the impact of these residues on human health or on the downstream sector (in particular cheese processing). As a result, many of these alternative or complementary products contain substances for which there is no Maximum Residue Limit (MRL). It is therefore normally forbidden to prescribe and administer them to a production animal, all the more so with a withdrawal period of zero!

– on efficacy: the results of the available studies do not yet allow a definitive conclusion to be drawn on the efficacy of these therapeutics, particularly as the exact composition of the active ingredients often varies from batch to batch. However, it seems that the effects are partial at best, encouraging fraudsters to optimise their therapeutic action, as was the case with fipronil in 2017; in this case, a herbal product used to control red lice in poultry fraudulently contained fipronil, an acaricide/insecticide that has no MRL and is therefore banned in hens producing eggs for human consumption.

– on marketing: their sale remains free, without veterinary prescription, i.e. anyone can declare themself a specialist without any special training or proof of competence.

There is currently a vacuum into which many unscrupulous laboratories have ventured. An Anses opinion and report (reference 2020-SA-0083) dated 8 December 2021 concerns the proposal of a methodology for assessing the risks to human health of herbal products (including essential oils) used in farm animals.

Anses proposes that the methodology described in its report should allow the classification of herbal products into one of the following three categories: i) a preparation that can be used in veterinary medicine without risk to the consumer; ii) a preparation that is considered, on the basis of the available data, to be of potential concern to the consumer; iii) a preparation that cannot be used in veterinary medicine because of the existence of a concern to the consumer. It should be emphasised that talking about products used in phytotherapy or aromatherapy immediately brings them under the definition of a medicinal product "by presentation", and unfortunately many people are not aware of this. It is now time to develop the regulations for products used as complementary and alternative practices and to provide high quality training for both breeders and veterinarians.

For example, if the withdrawal period for drug X administered to a lactating cow is 48 hours, this means that the farmer must discard the milk from the four milkings following the last administration of the drug (in a traditional system of two milkings per day); the milk produced by this cow can only go to the tank, and therefore marketed, from the fifth milking following the last administration of the drug. The WP refers to a veterinary medicinal product and may be different for two medicinal products containing the same pharmacologically active substances, for example because their excipients are different.

■ 1.4. Prescription and drug delivery

One of the characteristics of medicinal products is that their marketing is highly regulated and their sale and use are not free. For the breeder, to obtain a medicinal product, regardless of where it is purchased, a **prescription** issued by a veterinarian is required, with a few very rare exceptions (the requirement for a prescription or not in France is available on the ANSES website for each authorised medicine, http://www.ircp.anmv.anses.fr/). The **prescription** is an act of a medical nature with curative, prophylactic, metaphylactic or even zootechnical aims, ordering the implementation of care for animals. This prescription requirement also applies when the veterinarian administers the medicinal product to the animal himself. The prescription must include a number of mandatory details, in particular the withdrawal periods applicable to production animals.

The veterinary prescription is generally issued after a clinical examination or necropsy. It may, under certain conditions, be made without a clinical examination or an autopsy in the case of production animals (ruminants, pigs, poultry, rabbits and fish) and equids. In order to prescribe "without clinical examination", the veterinarian must carry out health monitoring on a limited number of animals (quotas fixed per veterinarian and per animal species) and realize:

– an annual health inspection of the farm, with a written report

– a written treatment protocol for each disease that the farmer may treat without a veterinary visit for the coming year;

– at least one follow-up visit between two annual inspection visits.

A 23-page appendix to the decree of 24 April 2007 sets out the minimum requirements for this monitoring for each of the ten animal sectors, including the health data to be collected during the annual health check in order to establish the resulting care protocol. The health check and the care protocol are signed and dated by the veterinarian and the breeder. The originals of these two documents are filed in the farm register and kept for five years.

The **dispensing** of medicines is a pharmaceutical act whereby the person fulfilling the prescription, a beneficiary, gives (delivers) the prescribed medicinal products to the person presenting the prescription. In France, the beneficiaries are

– the pharmacist who owns a pharmacy: they can dispense any veterinary and human medicinal product; we speak of a full practice;

– the veterinary practitioner: they may only dispense veterinary drugs (veterinary MA). However, their authorisation to dispense is limited to animals for which they are personally responsible or whose health monitoring and care are regularly entrusted to them, provided that the medicinal products are related to this monitoring or care;

– the pharmacist or veterinarian of a certified group: in this case, the supply is limited, on one hand to the compulsory prescription medicines on a positive list and, on the other hand to the non-compulsory prescription medicines within the framework of a Livestock Health Programme (LHP) granted to the approved group;

– the manufacturer of medicated feedingstuffs, only for medicated feedingstuffs that no longer have medicinal status as of 28 January 2022.

In 2020, veterinarians delivered about 79% of the veterinary medicinal products in France, pharmacists about 6% and groups about 15% (AIEMV, 2021). The dispensing of medicinal products requires, in addition to a paper or electronic record, specific information on the prescription and the medicinal product prescribed.

2. A veterinary pharmacy: why?

2.1. The farm pharmacy

The farm pharmacy is the farmer's pharmacy. It is based on a number of important principles: to have the medicines deemed necessary for the health of the animals (see Part 2.2) available in accordance with the regulations (see Part 1), to ensure that they are well conserved and to have the necessary and appropriate equipment for their administration (e.g. needles or drench guns). Thus, the farm pharmacy, dedicated exclusively to the animals of the farm, must be clean, tidy, closed, protected from dust, light, frost and temperature variations for medicines stored at room temperature (see photos 1 and 2). It is essential to maintain the cold chain for medicines stored between 2 and 8°C. The farmer should regularly check and dispose of expired medicines. The management of health care waste (expired medicines, needles, empty containers, etc.) is also a legal obligation: it must be stored, collected and disposed of in a specific way.

For the breeder, the use of veterinary medicines is subject to considerable administrative constraints to ensure that they are used in accordance with the regulations. Thus, by ministerial decree of 5 June 2000, it was made compulsory to keep a **breeding register**. This is the responsibility of the breeder. The breeding register improves the traceability of animal movements, the traceability of health and the transparency of the use of medicines. Within the register, there is a compulsory **health logbook** which ensures the traceability of the treatments carried out by the farmer or the veterinarian: all treatments administered to the animals are rigorously recorded, with the date of the treatment, the identification of the animal(s) treated, the start and end dates of the treatment, the medicine used (dosing regimen, route of administration, persons involved), the withdrawal period and any observations. In addition, the original prescriptions must be kept in the farm register for at least five years.

2.2 Major drug families

The drugs classically used in veterinary medicine can be divided into several large families (see Figure 1):

– Antiparasitics: These accounted for 31% of drug sales in 2020 in France (AIEMV, 2021). This category includes the control of internal parasites (nematodes, cestodes, trematodes, protozoa including coccidia) and external parasites (insects, mites). This category of drugs is very widely used because parasitosis is very common and very detrimental to livestock (mortality, growth retardation, disease). Resistance to antiparasitic drugs is developing, although the situation remains generally under control, with a few exceptions (see below). The lack of credible alternatives to drugs for the control of certain parasitoses sometimes makes it difficult to reduce the use of antiparasitic drugs, the main measure to limit the development of resistance. In addition, the use of pasture, or even the return to pasture for certain productions in response to societal demand, inevitably leads to an increased need for antiparasitic products. New tools are being developed to manage the risk of pest control for the various species, and recommendations are gradually changing towards less systematic use.

– Vaccines: they accounted for 24.5% of drug sales in 2020 in France, and their sales will increase (AIEMV, 2021). The development of prevention in livestock farming, particularly through the use of vaccines, is part of the ecoantibio2 plan launched in 2017 to reduce the risk of antibiotic resistance in veterinary medicine. Increasing the use of this type of medicine is therefore very encouraging for the development of more sustainable livestock farming. The limitations of the use of vaccines are well known: i) the price, which can be perceived as a large part of the drug budget: the economic balance is generally very much in favour of vaccination compared to the costs of certain infectious

Photo 1. ***A well-maintained farm pharmacy: the date of opening is marked on opened bottles, and storage ensures that medicines are well preserved.***

Photo 2. ***Example of a farm pharmacy that does not ensure the proper storage of medicines: in particular, the sterility of injectable medicines is no longer guaranteed.***

diseases. However, some of these costs are sometimes difficult for farmers to quantify (loss of growth, reproductive problems, extra work, etc.) and are therefore not always taken into account in their analysis; ii) the workload involved in vaccination; iii) the time taken to establish immunity, which discourages its use when animals are introduced into certain specific animal rearing sectors.

– Antibiotics: they accounted for 9.5% of drug sales in 2020 in France (AIEMV, 2021). In terms of live weight treated, the most commonly used families are tetracyclines (23.47%), penicillins (22.59%), aminoglycosides (11.82%), macrolides (11.05%), sulphonamides (8.88%) and polypeptides (8.77%) (Anses, 2021). The ALEA (Animal Level of Exposure to Antimicrobials) indicator, which refers to the percentage of treated animals in the total animal population, is classically used to assess antibiotic exposure. For example, an ALEA of 0.2 for a given species means that 20% of the total live weight of that species has been treated with antibiotics. In order of decreasing ALEA, the calculated antibiotic exposures in 2020 for the different species are as follows: Rabbit = 1.910; dog/cat = 0.659; pig = 0.491; sheep/goat = 0.363; poultry = 0.358; cattle = 0.255; horse = 0.220; fish = 0.164 (Anses, 2021).

The use of antibiotics in veterinary medicine has been greatly reduced in recent years in line with the ecoantibio1 and ecoantibio2 plans. In 2020, compared to 2011, the reference year, ALEA decreased for all species: -22.5% for cattle, -55.5% for pigs, -64.4% for poultry, -39.9% for rabbits (Anses, 2021). Moreover, certain categories of so-called critical antibiotics (third- and fourth-generation cephalosporins, second- and third-generation fluoroquinolones) are now used only as a last resort and their use in the field has collapsed (they now represent less than 0.5% of treatments in terms of live weight treated) (Anses, 2021). It should be noted that since 2017, in Europe (29 countries), thanks to efforts to reduce the use of antibiotics in veterinary medicine, the average consumption of antibiotics by humans (130 mg/kg) is higher than the average consumption of antibiotics by livestock (108.3 mg/kg) (ECDC, EFSA and EMA, 2021).

– Anti-inflammatories and analgesics: This category of medicines has seen an increase in use in recent years with the new recommendations on animal welfare management (dehorning, castration, painful diseases). We do not have data on the volume of sales they represent (< 10%).

The **other categories** are insignificant in terms of sales volume:

– Reproductive cycle medicines: mainly hormones to stimulate, synchronise or block reproduction in farm animals.

– Drugs for rehydration and metabolic syndrome

– Anaesthetics

– Euthanasia

– Medicines for major functions (digestive, renal, etc.)

– other

Overall, if we compare 2020 with 2019, the sale of drugs decreased by 2.58% for poultry and 1.34% for ruminants, but has increased by 0.99% for pigs (giving an overall decrease of 1.08% for production animals) (AIEMV, 2021). At present, these figures are not very meaningful because the objectives may differ according to the families of medicines concerned. For example, it is now recommended to reduce the use of anti-infectives (antibiotics and antiparasitic agents), mainly in order to reduce the selection and spread of resistant organisms. On the other hand, farmers are encouraged to increase the use of vaccines, but also to use analgesics when animals are in distress (illness, surgery) in order to guarantee respect for the five fundamental freedoms for animals, as defined by the FAWC (Farm Animal Welfare Council).

■ 2.3. Different uses of drugs

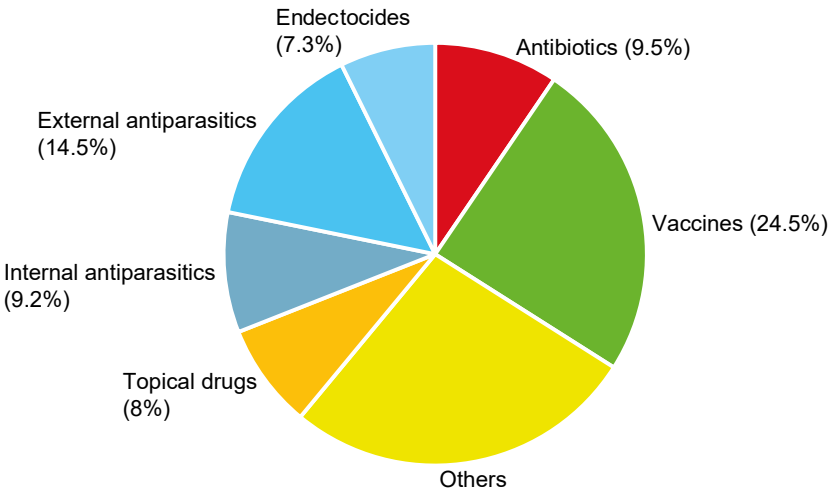
In animal husbandry, treatment is most often collective. Different strategies coexist with regard to the use of drugs:

– Curative treatment: the animal is seen to be ill and the treatment of this illness is a matter of necessary animal care, always respecting the five fundamental freedoms mentioned above. This treatment may be individual or collective if several animals are affected, for example by a bacterial, fungal or parasitic infectious agent.

– Vaccine prophylaxis: this use refers only to the use of vaccines to prevent bacterial, viral, parasitic or fungal infections. Prophylaxis is the set of measures taken to prevent the occurrence of diseases. It usually consists of a sanitary/zootechnical component, in particular biosecurity, i.e. the use of "shielding measures", to draw a parallel with the COVID-19 crisis, and a vaccination component, if it exists. Vaccination is mainly a collective approach, although it can sometimes be individual (e.g. tetanus in horses). It makes it possible to strengthen the animals' defences and thus limit the clinical or zootechnical consequences of infections. However, vaccination must generally be combined with sanitary or zootechnical measures in order to achieve its full potential. For example, young grazing cattle that have been correctly vaccinated but are housed in a building that is not adapted to their needs (poor air renewal, draughts or heat stress) will remain very susceptible to bovine respiratory diseases. Finally, prophylactic vaccination should ideally be carried out before the period when the herd is at risk of disease, especially since the development of immunity in the animal after vaccination is often quite long (around a few weeks). In certain specific situations and for certain vaccines, vaccination of animals during the risk period or at the same time as sick animals can be carried out with convincing results (e.g. vaccination against colibacillosis in laying hens).

– **Preventive or prophylactic treatments**: Treatments are applied at a certain point in the production cycle, whether or not there are sick animals on the farm. For example, prophylactic treatments against gastrointestinal strongyles are very often administered to young cattle when they are put out to pasture, to limit parasite recycling during grazing and thus future infestations that would be detrimental to the animals' health and growth. Antibiotic prophylaxis, based on the same principle, is sometimes used to limit morbidity and mortality associated with respiratory or digestive diseases in the days or weeks following batching or weaning in pigs or cattle. In US cattle feedlots, a meta-analysis estimated that antibiotic prophylaxis improved average daily gain (ADG) by 0.11 kg/d (Wileman *et al.*, 2009). However, depending on the batch of cattle, the number of cases prevented by this measure does not always compensate for the additional cost of treating the whole batch (Nickell *et al.*, 2008). Furthermore, this preventive use of antibiotics is highly criticised as it contributes to the massive use of antibiotics, which facilitates the selection and spread of antibiotic-resistant strains (Schwarz and Chaslus-Dancla, 2001; McEwen and Fedorka-Cray, 2002; Phillips *et al.*, 2004). Antibiotic prophylaxis is not a feasible measure in a sustainable management framework (Scientific Committee on Animal Health and Animal Welfare, 2001). It has been banned in France since 28 January 2022 (except in very specific cases). The implementation of sanitary and vaccination measures should be the first priority (Anses, 2014). It should be noted that certain families of so-called critical antibiotics are completely banned for prophylactic use.

Figure 1. ***Distribution of drug sales in 2020 by major therapeutic class in veterinary medicine in France, all species (from AIEMV, 2021).***



– Metaphylactic treatments: These treatments consist of treating both clinically ill animals and animals in the same group that are still clinically healthy but have a high likelihood of being infected due to close contact with sick animals (EMA, 2016). This highly regulated concept is specific to the European Union, as other countries do not always make such a clear distinction between prophylaxis and metaphylaxis. This treatment strategy is a practice that is developing in batch farms as an alternative to antibiotic prophylaxis, precisely with the aim of reducing the use of antibiotics by treating only when the disease is actually present. The main objectives are to control working time (it is easier to treat all animals at once) and to provide early treatment to maximise the effectiveness of antibiotic therapy, reduce the risk of relapse or chronicity and compensate for under-detection. The choice of metaphylaxis should be made by the veterinarian, who is best placed to judge its relevance based on his knowledge of the disease, its epidemiology, its severity and also his knowledge of the farm.

– Growth promoters: these are orally administered antibiotics, usually in a dosage regimen that uses lower doses than those used for other types of treatment. The aim is to maximise the zootechnical performance of the animals. This use has been banned in Europe since 2006.

There are a number of factors to consider when choosing which drugs to use. In the pig, poultry, rabbit and veal calf industries, the concept of margin (cost/benefit) is essential and sometimes the use of antibiotic therapy is more economically interesting than other more sustainable measures. For example, hyperthermia is the earliest sign of respiratory disease in cattle, but it is impossible for a farmer armed with a simple thermometer to take the temperature of all his animals every day, hence the interest in using metaphylaxis when the health situation deteriorates. Automated monitoring tools are being developed, but these systems are still too expensive or not reliable enough.

3. Future issues relating to veterinary pharmacy

■ 3.1. A deteriorating image of veterinary medicine in animal husbandry

Looking at the latest marketing campaign of the retailer Carrefour, "Act for food", the message is striking: Carrefour is doing away with antibiotics in all its "Carrefour quality" products. The basic message is attractive, with a focus on the joint prevention work the retailer is proposing with its contracted farmers (available on a dedicated website). Unfortunately, the limited advertising form that reaches the majority of consumers can be summarised as follows: livestock farming uses too many antibiotics, while there are other ways, thanks to the supermarket (!). This campaign clearly illustrates the gap between the efforts made in France (45% reduction in the use of antibiotics in animals in eight years, all sectors combined (source: DGAL November 2020), see section 2.2) and the image perceived by the general public of an agriculture that is too industrialised and out of touch with the major issues of the day. This image deficit is highly detrimental to all livestock sectors and demotivating for those involved, who do not see their efforts pay off.

Similarly, the general public is still confused about the reality of the use of drugs in livestock farming in France. For example, the use of growth hormones or antibiotics as growth promoters is strictly prohibited in Europe, whereas this is not the case everywhere, particularly in the United States. Communication about drugs by professionals to the general public is highly regulated and generally limited to a discourse that is rather opaque to the uninitiated. The lack of clear communication to the general public encourages the dissemination of disturbing messages by antipharmaceutical lobby groups, particularly on social networks, messages that contribute significantly to the deterioration of the image of the entire sector. This is all the more true as many of the medicines include vaccines that are essential for the sustainable control of infectious diseases in livestock.

On the other hand, so-called alternative products, presented as natural (phytotherapy, aromatherapy), are over-promoted and therefore enjoy a very favourable image among the general public and breeders. However, these new therapies raise many questions about their quality, their harmlessness to the animal or the consumer, or their efficacy, especially when compared to the requirements applied to medicinal products (see Box 3). In addition, the lack of an appropriate regulatory framework leads to a complete lack of transparency on on-farm use, which complicates risk management and diverges from current market and consumer demands. A new health scandal would certainly not improve the image of French livestock farming.

■ 3.2. Fighting resistance to anti-infectives

Among anti-infectives, the main distinction is between antibiotics and antiparasitics. The fight against the development of resistance to anti-infectives is now essentially a matter of reducing their use, with measures that are either restrictive (for antibiotics) or based on the good will of the various players (for antiparasitics); a sort of double standard.

The fight against antibiotic resistance is global and involves various international (UN, WHO, OIE), regional (EMA, FDA) and local (Ministry of Health and Ministry of Agriculture in France) organisations. The "one health" approach has been democratised, recognising that animal, human and environmental health are interlinked. In fact, therapeutic failures related to antibiotic resistance in animals are rare. The measures taken in veterinary medicine are first and foremost a response to a public health problem. Two principles are therefore applied: the precautionary principle for risk assessment and the prohibition principle for risk management. However, a quantitative risk analysis, which would have allowed a ranking of the main risk factors, was rejected by WHO experts, who

considered that a plausible risk was sufficient for the application of the precautionary principle (Toutain *et al.*, 2014). Thus, the contribution of veterinary medicine to the development of antibiotic resistance in humans is unknown. Two main risks have been identified:

– Transmission of resistant zoonotic agents to humans by direct contact or via food: this is an individual risk, primarily affecting professionals in the agri-food sector. The final consumer may also be affected locally.

– Amplification of resistance genes in animals and their effluents, leading to their spread in different ecosystems: this is a global ecological risk, with exchange of resistance genes between human, animal and environmental commensal bacteria. This risk appears to be the most important because it is difficult to contain.

The strategy adopted at global level is mainly based on reducing the use of antibiotics in veterinary medicine, with particular emphasis on certain families of critical antibiotics (banning or severely restricting their use).

The fight against resistance to antiparasitic drugs is essentially a veterinary issue, since in so-called "developed" countries there are few parasitoses that affect human health (which is not necessarily the case in the South). Consequently, the resources available are much smaller and international coordination is essentially limited to the regional level (the European Union in our case). The main resistances causing difficulties in livestock farming today are resistance to nematodicides in small ruminants and in equids, and even resistance to anticoccidials in poultry or resistance to certain arthropods (SNGTV/OIE Colloquium, 2017). Rational use of pesticides is essential for the future of certain productions. Some uses will therefore have to change.

■ 3.3. Animal welfare

Animal welfare is a recent but essential issue in livestock farming, not only to guarantee the quality of marketed products (stress is detrimental to the quality of meat, for example), but above all to meet new social demands. It was not until 28 January 2015 that the Civil Code in France recognised animals as "sentient beings" (article 528), even though this concept already existed in the Rural Code. Farm pharmacy plays an essential role in the management of pain. In contrast to anti-infectives, the use of analgesics must be encouraged. The increased use of anti-inflammatory drugs for pain relief during dehorning or calving in cattle and during farrowing in sows illustrates this change in mentality. Regulations are also changing rapidly, forcing farmers to change certain practices. For example, castration of piglets has been banned since February 2022 unless a local anaesthetic and anti-inflammatory are used. The other alternatives are (1) no castration (but this results in less fatty meat, more aggressive animals and a risk of urine odour when cooking for some whole males) or (2) the use of a vaccine that temporarily blocks testicular function. The consideration of animal pain is now accompanied by an incentive, or even an obligation, to change certain practices and to relieve the suffering animal.

■ 3.4. Ecotoxicity and biodiversity

Considering the impact of medicines on the environment, non-target organisms and biodiversity is a new but fundamental issue for the sustainability of livestock production. Civil society is now particularly sensitive to this issue, with particularly active associations. For example, the lifting of the ban on neonicotinoid pesticides in beets in 2020 has sparked a heated debate in France because of the environmental impact of these insecticides, particularly on pollinating insects. Another example of this phenomenon is the increase in the number of Natura 2000 sites. Natura 2000 sites are a key instrument of European biodiversity policy. Their aim is to take better account of biodiversity issues in human activities. In these special areas, restrictions on the use of certain drugs can have an impact on veterinary prescriptions. This is the case, for example, with macrocyclic lactones or pyrethroids, two antiparasitic molecules widely used in ruminants to treat nematodes or flies/ticks during the summer season. In these particular areas, these molecules sometimes have to be replaced by others that are less ecotoxic (but there are few credible alternatives), or they have to be used in conjunction with animals being kept indoors for varying lengths of time, which does not correspond to the summer use of pastures!

In 2007, the European REACH Regulation (Regulation 1907/2006) came into force to safeguard the production and use of chemical substances in European industry. This regulation required a census of all chemical substances manufactured or imported on the European market (to be completed in 2018), followed by an evaluation of these substances' hazards, with the aim in particular of protecting human health and the environment and providing identical and transparent information to all. This regulation now also applies to certain active substances in drugs, and in particular to substances of very high concern: these are substances that are persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB). As of 2017, all medicines seeking marketing authorisation must be assessed to determine whether they belong to one of these two categories (EMA CVMP, 2015). Specifically, if a substance belonging to one of these categories does not provide a significant benefit compared to what is already on the market, its authorisation will be refused. In 2018, for example, the first veterinary drug was refused authorisation because of an environmental risk: Longrange®, a long-acting eprinomectin (EMA CVMP, 2018). For drugs already on the market, the classification as a substance of very high concern has been completed and nearly 20 molecules have been identified, all of them antiparasitic. To date, none of these substances has been withdrawn, but some are being studied, in particular to better characterise their environmental impact under field conditions, and also to evaluate the alternatives available in the event of withdrawal. Special precautions for use have been included in these products' package leaflets, indicating the

specific ecotoxicity of these molecules and the non-target organisms affected, as well as certain restrictions on use (e.g. restriction of access to watercourses for a certain period). The long-term objective of this Regulation is to ban the molecules identified as being of very high concern and to replace them with molecules that are less hazardous to the environment. Unfortunately, for certain indications, particularly insecticide or acaricide treatments, there is no credible alternative that is not highly toxic to the environment. Therefore, the most rational use should be encouraged, especially for these molecules. The veterinarian should be the leader and guarantor of this rational use, applying the new recommendations from research centres on sustainable pest management. In the field, the situation remains more contradictory, as knowledge in this area is insufficiently shared. Moreover, this sometimes clashes with health needs, as in 2008 during the bluetongue crisis, which is still ongoing and which led to the obligation to massively disinsectize animals and the lorries transporting them, a measure whose results in terms of managing the bluetongue crisis remain controversial, even though these highly ecotoxic insecticides were used *larga manu*.

■ 3.5. Charters and labels

There are various charters and labels in animal husbandry today that will have an impact on the prescription of medicines. The best known is the "organic production or farming" label, an official label that meets legal requirements. There are many others, which may be private and meet their own specifications. To be eligible for organic certification, livestock farms are subject to the following restrictions on veterinary treatments (Official Journal of the European Union, 2018):

– Any preventive treatment, including anticoccidial treatment, or treatment to control reproduction (induction or synchronisation of oestrus) is strictly prohibited.

– No restrictions on the use of vaccines

– Control of pest control treatments (depending on the species)

– With the exception of vaccines, parasite treatments and compulsory eradication plans, a maximum of 3 curative allopathic treatments may be administered in a rolling 12-month period. The number of treatments allowed is reduced to one for each production cycle of less than 1 year.

– The applicable withdrawal period is twice the legal withdrawal period used in conventional farming, with a minimum of 48 hours.

Some comments from the authors on these labels:

First of all, the doubling of withdrawal periods for organic labels does not have a solid scientific basis, since the withdrawal periods in veterinary medicine are already determined with very strict postulates. The main aim of this option is to discourage the use of allopathic treatments unless they are absolutely necessary, a virtuous philosophy. However, the limited number of treatments available and the longer waiting times can also have perverse effects, particularly in the therapeutic management of pain. In monogastric production, with short production times, this pressure to treat once may also delay the implementation of a necessary antibiotic treatment, thus increasing treatment failures, relapses or animal suffering (early treatment is often essential for the effectiveness of antibiotics). There is even an extremist minority among organic farmers or those who do not use antibiotics who refuse to use any allopathic medication, with the result that suffering animals are denied treatment that is essential to their health. The risk of the demedicalisation of farm animals exists today in these labels, whose original philosophy was a return to more sustainable production and better consideration of animal welfare. The rigidity of the charters and labels sometimes goes against the common sense of the breeder and can make it difficult for the farmer to provide the necessary care for their animals.

Conclusion

Veterinary pharmacy is an important part of farm animal health and welfare management. Today it is criticised because it is not well understood, especially by the general public. Firstly, it is multifaceted, and while it is desirable to reduce the use of anti-infectives to what is strictly necessary, it is important to promote the use of vaccines, anti-inflammatories and analgesics. Secondly, it is highly regulated and relies on a network of trained professionals, which allows real control of practices by public services and traceability, which ensures consumer protection. Finally, it is an important financial issue, as France is the leading EU country in terms of the volume of sales of veterinary medicines.

The correct use of medicines remains essential for more sustainable farming. Although there are still many battles to be fought, knowledge to be acquired and practices to be changed, many things have already been put in place with very convincing results, which is very encouraging for the future. What remains is to better communicate these efforts to the general public, so that every citizen can remain proud of the French livestock industry.

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Abstract

In Europe, veterinary medicines can only be marketed following a marketing authorisation (MA) granted by a competent authority and based on a rigorous scientific evaluation of their quality, efficacy, safety and residues in food. Sales are also highly regulated, with a central role of the farm veterinarian and a strict traceability system to ensure consumer protection. Veterinary pharmacy is a key part of farm animal health and welfare management, and the correct use of medicines remains essential for sustainable livestock farming. The use of antimicrobials must thus be reduced to the strict minimum to prevent the selection and spread of resistance genes. Furthermore, the use of vaccines, anti-inflammatories or analgesics to control infectious diseases or improve animal welfare should be encouraged. Sometimes, due to the ecotoxicity of some drugs or the existence of specific labels, new animal health management strategies have to be developed. In all these areas, even if there is still a lot of new knowledge to be acquired, practices to be changed or alternatives to be developed, French livestock farming has made great progress in recent years. What remains to be done is to communicate to the general public, who often still have a very poor image of the use of medicines in livestock farming.

Résumé

La pharmacie vétérinaire – un enjeu majeur pour un élevage durable

Le médicament vétérinaire n'est pas un produit comme les autres. Ainsi, il ne peut être commercialisé qu'après obtention d'une Autorisation de Mise sur le Marché (AMM), fondée sur une évaluation scientifique stricte de sa qualité, de son efficacité, de son innocuité, et des résidus retrouvés dans les denrées alimentaires, par une autorité publique compétente. De même, sa commercialisation est très encadrée, avec un rôle central du vétérinaire de l'élevage, et une traçabilité rigoureuse qui assure une protection efficace du consommateur. La pharmacie vétérinaire est une composante clé de la gestion de la santé et du bien-être des animaux d'élevage. Bien utiliser le médicament reste indispensable pour un élevage plus durable. Ainsi, il faut réduire l'usage des anti-infectieux au strict nécessaire, dans un environnement de lutte contre la sélection et la diffusion de gènes de résistances. A contrario, le recours aux vaccins, aux anti-inflammatoires ou aux antidouleurs doit être absolument encouragé pour lutter contre les maladies infectieuses ou améliorer le bien-être animal. Parfois, à cause de l'écotoxicité de certains médicaments, ou de par l'existence de chartes et de labels spécifiques, de nouvelles stratégies doivent être mises en place pour la gestion de la santé des animaux. Dans tous ces domaines, même s'il reste encore beaucoup de connaissances nouvelles à produire, de pratiques à changer ou d'alternatives à mettre au point, l'élevage français a fait de grands progrès ces dernières années. Reste à communiquer auprès du grand public qui conserve une image très dégradée du médicament en élevage.

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