European conference on the use of plants in veterinary medicine 29 March 2022

SUMMARY

In France, the use of herbal products is in full expansion. In livestock animals, the use of essential oils, plants or plant-based preparations is a response to the development of organic breeding, to a societal request and to the European Farm to Fork and Green deal strategy.
To date, only five herbal veterinary medicinal products for dogs and cats have a marketing authorization in France and two for food-producing animals. The large majority of the plant-based products used have not been assessed under Regulation and therefore cannot currently be used in veterinary medicinal products intended for food-producing animals or be prescribed by a veterinarian as part of the "therapeutic cascade" Despite the claim for these products are therapeutics, many plants based specialties are often administered to animals as a feed supplement or feed additives.

At Anses, the French agency for veterinary medicinal products (Anses-ANMV) has been working since several years to improve the number of herbal VMPs.
Based on this context, Anses-ANMV decided to make this topic a main theme of the French Presidency in veterinary medicine. We organized in March, a conference on the use of plants in veterinary medicines to arise awareness of the problematic of use of such products in veterinary medicine.

The conference was held in several sessions:

Session 1 – Contextualisation on the use of plants in veterinary medicine in the European Union

Practices analysis and regulation mode in France
F. Latrèche, Anses-ANMV

The role of plants in organic livestock production systems
M. Walkenhorst, FIBL & M. Calmels, IFOAM

Veterinarians' views
I. Lussot, RéPAAS

Opinions and recommendations of EU manufacturers of animal health products
R. Clayton, AnimalhealthEurope

Session 2 - Feedback on the issues encountered in the authorisation of herbal medicines for human use compared with conventional chemical medicines

General presentation and regulatory response illustrated with concrete examples
A. Lê, ANSM

Austrian experience with traditional herbal medicinal products – Quality, clinical and regulatory requirements on the dossier
R. Länger, BASG

Session 3 – Work done by France

French regulation and Anses reflection on the scientific evaluation of herbal veterinary medicines

S. Barreteau, Anses-ANMV

Prospects at European level

How to centrally authorise Herbal Veterinary Medicinal Products and setting of MRLs?

J. Torren Edo, EMA

European Commission intervention

E. Zamora Escribano

Session 1 – Contextualisation on the use of plants in veterinary medicine in the European Union

Practices analysis and regulation mode in France (F. Latrèche, Anses-ANMV)

The fight against antibiotic resistance, the increase of organic farming and the need for changes in breeding practices have led to a strong demand for alternative therapies, including phytotherapy and aromatherapy. The high level of demand for herbal products and essential oils is nevertheless met by a limited supply.
The analysis of the information gathered through the thirty-three (33) interviews conducted with the various stakeholders (breeders, veterinarians, suppliers, French veterinarian statutory board, etc.) highlights, on the one hand, the desire of breeders for autonomy through the use of phytotherapy and aromatherapy and, on the other hand, the need for a framework for herbal product and essential oils ranges marketed for external use with therapeutic claims.

The role of plants in organic livestock production systems (M. Walkenhorst, FIBL & M. Calmels, IFOAM)

The intake of an incalculable amount of known or unknown phytochemical substances via pasturing or outdoor running livestock could be assumed based on diverse European pasture agro-ecosystems. Animals even self-medicate with plants (Villalba et *al.*, 2017). There is a rising evidence that meat and milk produced based on biodiverse pastures is healthier than beef from feedlots (Provenca et *al.*, 2019; van Vliet et *al.*, 2021). The veterinary use of medicinal plants to treat animals has a long tradition (Hippiatrika, 300; Delafond, 1855; Fröhner, 1900; Steck 1944). European farmers recently use more than 450 different plant species to treat livestock (Mayer et *al.*, 2014), often in consistency with historical literature (Stucki et *al.*, 2019; Schlittenlacher et *al.*, 2022).

Approximately 2'000 European veterinarians of AT, FR, DE, ES, CH and NL show recently interest in further education in veterinary herbal medicine and e.g. more than one third of German veterinary practitioners regularly use herbal veterinary medicinal products (VMP). Officially recognised further education titles in veterinary herbal medicine exist in AT, DE and CH. Research (including pharmacology) in the veterinary use of medicinal plants is conducted in AT, CH, ES, NL and PL. An international scientific network about medicinal plants for animal health[1] is active since about 10 years. Around 10 European enterprises produce still more than 20 registered herbal VMP for livestock and companion animals for the national markets. Some of them are on these markets since more than 50 years. Because the new EU Regulation (EU) 2019/6 on VMP regulates not explicitly herbal VMP these well-tried and much used products are in danger to disappear.

Organic husbandry respects natural interrelationships and promotes biodiversity (e.g. on pastures), animals natural behavior and pasturing. It intends to protect animal health mainly through preventive measures. Herbal preparations shall be first line treatment of animal diseases to reduce the use of antimicrobials and other xenobiotic. Based on their plant specific multi-component compositions medicinal plants bear a potential to reduce the use of antimicrobials and other xenobiotics in veterinary medicine (Ayrle et *al.*, 2016; Farinacci et *al.*, 2021). Pragmatic solutions to enable European veterinary herbal medicine on a legal

[1] https://ga-society.org/activities/animal-health-network/

base with herbal VMP are highly needed. A toxicological assessment should take into account that medicinal plants are always complex mixtures of a broad spectrum of phytochemical substances. Within these mixtures the bioactivity of a single substance will be different compared to a single substance given alone.

Veterinarians' views (I. Lussot, RéPAAS)

In 2018 the three French veterinary technical organisations AFVAC[2], AVEF[3], SNGTV[4] created the RéPAAS[5]: a network of veterinarians working with herbal medicines, to respond to the growing demand for advice and support from farmers and pet owners for integrated management for livestock or animal health.

In France, farmers and animal owners use herbal products (feeds or dietary supplements, often a mixture of various plants of unknown quantity and quality), most of the time with no veterinary input or follow up, nor consideration about the maximal residue limits legislation.

Veterinarians are the only professional able to make an accurate diagnosis and ensure traceability and efficiency evaluation of their treatments, which is the only way to ensure safety, not only for users and their animals, but also for the potential consumers.

The veterinary profession needs to:

- lead the way forward in promoting scientifically based use of herbal medicine, relying on scientific evidence to prescribe herbal products,
- use products based on strict quality control process with documented harvesting, drying and storage procedures,
- implement and promote adapted and pragmatic legislation,
- invest in research and confirm the results of the first studies suggesting potential interest of herbal products as a way to deal with antibiotic resistances,
- share scientific and safety data with the human medical profession as part of the "One health" concept,
- implement public research funding as herbal products cannot be patented and thus private funding is very sparse.

The herbal products market is growing rapidly and will continue to grow whether the veterinary profession gets involved or not. If the current legislation does not change, farmers will carry on using herbal products without veterinary input with no reliable traceability.

In order to maintain safety (both for users and consumers) and animal welfare vets are essential to veterinary herbal medicine.

[2] AFVAC : Association Française des Vétérinaires pour Animaux de Compagnie
[3] AVEF : Association Vétérinaires Equine Française
[4] SNGTV : Société Nationale des Groupements Techniques Vétérinaires
[5] https://www.repaas.org/

Opinions and recommendations of EU manufacturers of animal health products (R. Clayton, AnimalhealthEurope)

The basic principles proposed by the industry are the following:

- A marketing authorization required for any product meeting the definition of a veterinary medicinal product by claim or function;
- Regulatory controls that must be proportionate to the benefit/risk and by means that least hinder enterprise;
- A marketing authorization is based on data demonstrating adequate quality (manufacturing), safety (patient, consumer) and efficacy;
- An harmonised approach at EU level;
- A broad range of therapeutic options in veterinary medicine.

Major challenges are:

- Cost of marketing authorization data dossier vs marketing value;
- Regulatory system ill-adapted for plant-based products;
- Lack of MRLs for herbal products;
- Difficulties in defining and demonstrating quality of plant-based products.

The proposed approaches for traditional herbal medicines used in animal health are a simplified registration system with, among others, an application file with reduced supporting data and to learn from the system for human herbal medicines.

Session 2 - Feedback on the issues encountered in the authorisation of herbal medicines for human use compared with conventional chemical medicines

General presentation and regulatory response illustrated with concrete examples (A. Lê, ANSM)

The Committee on Herbal Medicinal Products (HMPC) is the European Medicines Agency's (EMA) committee responsible for compiling and assessing scientific data on herbal substances, preparations and combinations. The HMPC establishes EU monographs covering the therapeutic uses and safe conditions of well-established and/or traditional use for herbal substances and preparations. HMPC also prepares scientific guidelines on quality, safety and traditional use or well established use to facilitate the harmonization of the requirements in the marketing authorization for the stakeholders and national competent authorities.

HMPC also drafts an EU list of herbal substances, preparations and combinations thereof, for use in traditional herbal medicinal products, which is mandatory after adoption by the EU Commission.

Nevertheless, the qualification of the product, the declaration of the active substances in each dossier, the data justifying the efficacy or the recognition of the traditional use, are critical points. Clarification of the above mentioned points are needed to promote the access to herbal medicinal products for the patients.

Involving patients for a reliable scientific communication on the risk and the appropriate use of the herbal medicinal products, using real world data or real world evidences, could add new understanding and viewpoints for this type of OTC medicinal products

Austrian experience with traditional herbal medicinal products – Quality, clinical and regulatory requirements on the dossier (R. Länger, BASG)

Dossiers for applications for marketing registrations of traditional herbal medicinal products (THMPs) for human use have to comply with the guidelines elaborated by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency. The required documentation of the quality of the starting materials, manufacturing processes and controls of herbal preparations and of the finished drug product are for all herbal medicinal products for human use identical, independent of their regulatory status. There are no simplifications acceptable for THMPs.

The non-clinical documentation in the dossier of THMPs should focus on a potential toxicity, particularly data demonstrating the absence of a risk of genotoxicity are required.

The clinical part of the dossier has to demonstrate the traditional medicinal use of the applied product. This can be achieved either with reference to an EU herbal monograph (established by the HMPC) or with reference to one or more corresponding products. For such corresponding products the products history over 30 years including details on the contained herbal preparations, the indication and the posology must be documented with suitable references.

The EU-wide harmonised view on the evidence on traditional medicinal use as published in the EU herbal monographs paved the way towards a successful implementation of the system. Meanwhile the majority of herbal medicinal products for human use are registered in this way in the EU.

Session 3 – Work done by France

French regulation and Anses reflection on the scientific evaluation of herbal veterinary medicines (S. Barreteau, Anses-ANMV)

Since 2016, the two main actions of Anses-ANMV are to:

1) **Promote the submission of marketing authorization applications for herbal veterinary medicinal products (Request No 2014-SA-0081[6])**
   The primary challenge for MA applications for these substances is the lack of an appropriate maximum residue limit (MRL) status for the large majority of plants of interest in veterinary medicine.
2) **Propose a MRL approach adapted to plants and essential oils (Request No 2020-SA-0083[7])**

A consumer risk assessment methodology, specific to plants and herbal preparations, including EOs, is proposed with a supporting two-step decision tree that can guide assessors throughout their assessment. This work is based on available data from monographs for herbal medicinal products for human use and assessments of plants in other regulations (food additives, animal feed, plant protection products…). This specific method classifies preparations into one of the following three categories:

- Preparation that can be used in veterinary medicine for food-producing animals without any risk to consumers. These preparations must be included on a list in order to be authorised in medicinal products intended for food-producing animals. There may be restrictions on use, for example concerning routes of administration;

[6] https://www.anses.fr/fr/system/files/MV2014SA0081EN.pdf
[7] https://www.anses.fr/en/system/files/ERCA2020SA0083EN.pdf

- Preparation considered as potentially of concern for consumers based on the available data (which means it cannot be used at the present time). A case-by-case assessment is necessary with the possibility of generating additional data or using the MRL approach.
- Preparation that cannot be used in veterinary medicine for food-producing animals due to concern for consumers.

In France the main next steps are:

- Creation of an Anses working group in order to apply the proposed methodology, establish lists of plants/EOs and prepare MRL dossiers for submission to EMA,
- Communication and training to vets and breeders.

In Europe, Anses-ANMV proposed to:

- Discuss this approach at the CVMP/CMDv presidency meeting in order to then ask a scientific question to CVMP (Art. 141 1 e),
- Submit a MRL dossier to EMA.

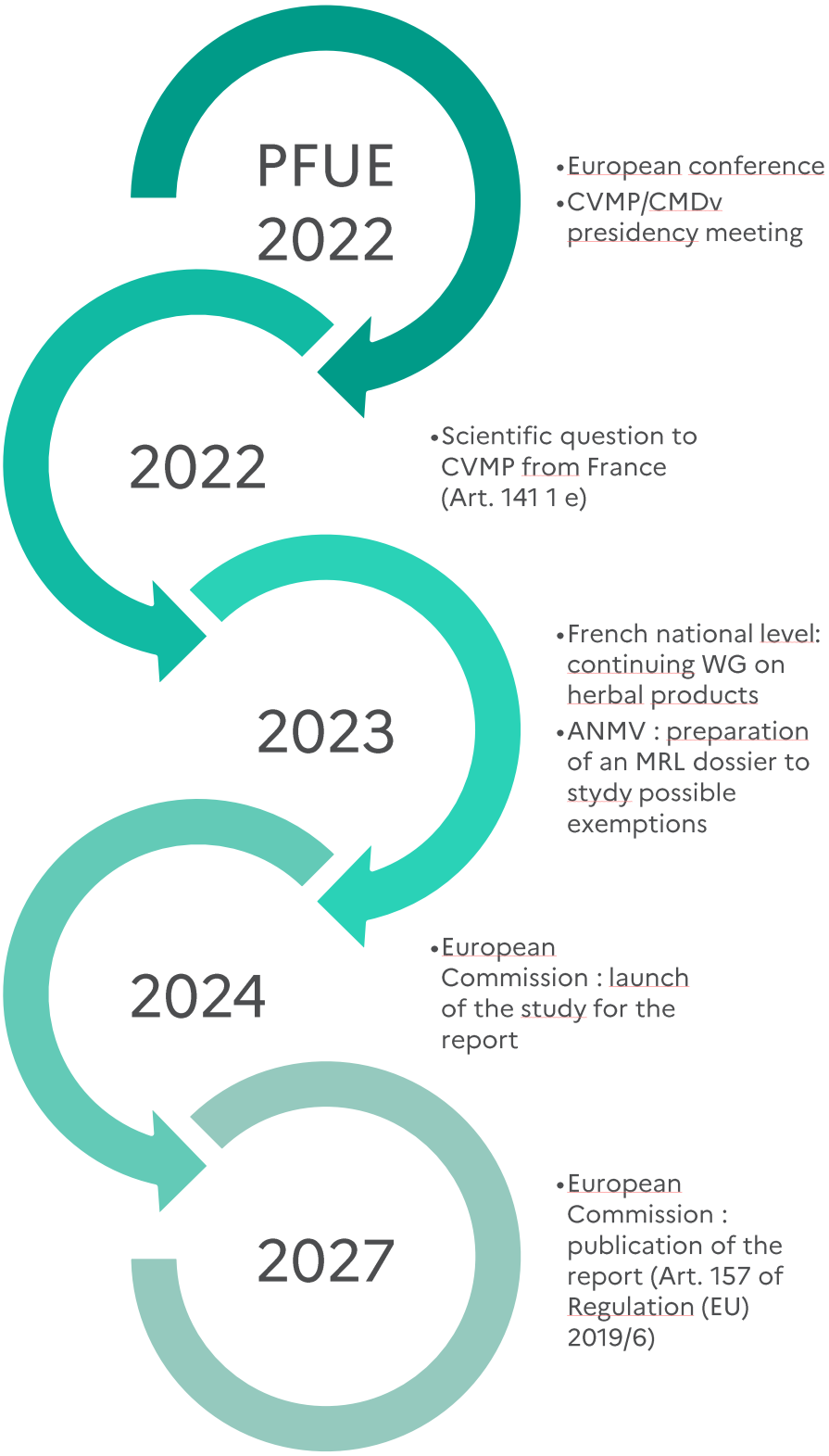
Prospects at European level

How to centrally authorise Herbal Veterinary Medicinal Products and setting of MRLs? (J. Torren Edo, EMA) and European Commission intervention (E. Zamora Escribano)

MRLs are one of the steps to achieve a marketing authorization but most MRLs for herbal products were set before 2000. To date, there is no specific guidance on how to set MRLs for herbal products or marketing authorisations for herbal products. In order to work on this, a scientific opinion of CVMP can be requested by Member States according to article 141 (1) (- e) of Regulation (EU) 2019/6. The aim would be to produce a guideline on how to simplify the MRL dossier and to set recommendations for the authorization of herbal medicinal products.

Article 157 of the Regulation indicate that by 2027, the Commission will have to produce a report to the European Parliament on traditional herbal products used to treat animals in the Union. If appropriate, the Commission shall make a legislative proposal in order to introduce a simplified system for registering traditional herbal products used to treat animals. Commission will commence to study to support the report in 2024 with an external contractor. This study planned to last about a year after awarding it. The final report of the supporting study will be used a starting point. Member State engagement will be key for meaningful results.

Next steps


PFUE 2022
•European conference
•CVMP/CMDv presidency meeting
2022
•Scientific question to CVMP from France (Art. 141 1 e)
2023
•French national level: continuing WG on herbal products
•ANMV : preparation of an MRL dossier to stydy possible exemptions
2024
•European Commission : launch of the study for the report
2027
•European Commission : publication of the report (Art. 157 of Regulation (EU) 2019/6)