

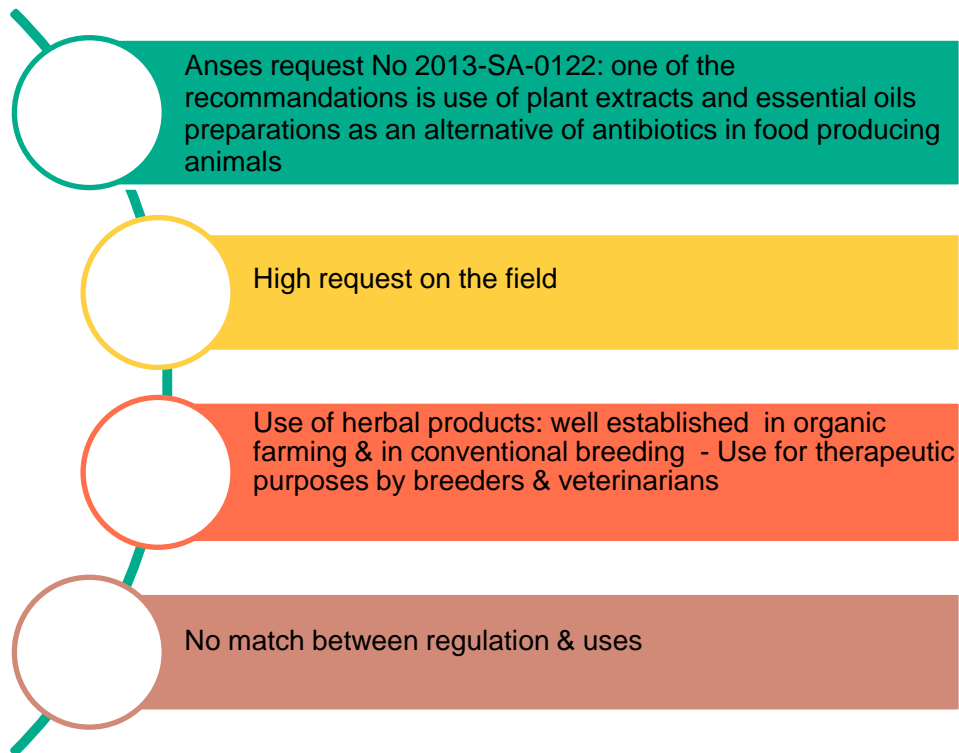
# EUROPEAN REGULATORY STANDARDS FOR HERBAL VETERINARY MEDICINAL PRODUCT

MedPlant4Vet – Training course  
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# 1. Background

## Background of the use of plants in France



# Background of the use of plants in France

## Herbal products most frequently used

Essential oils



Plants



Complementary feed



Hygiene products



# Background of the use of plants in France

## Plants could help decreasing the use of antibiotics

Many studies suggest that phytotherapy can be a useful tool in the treatment of infections via antimicrobial and anti-inflammatory properties.

Plants have antioxidant properties, stimulate immune system, inhibit inflammation, support quick removal of toxins from the body, prevent accumulation of bacterial pathogens.

A lot of feed back from use of plants and essential oil from the field either:

- Mainly in feed or water in intensive production (poultry, calves, pigs )
- topically or by oral use in cows.

Very few good clinical studies to prove the efficacy of phytotherapy  
Their interest and use may likely be mainly in prevention

# Background of the use of plants in France

## Use of plants and essential oils on the field

ANSES Study in organic chickens, Le Bouquin et al, 2017

Epidemiologic study survey on 85 organic chicken farms

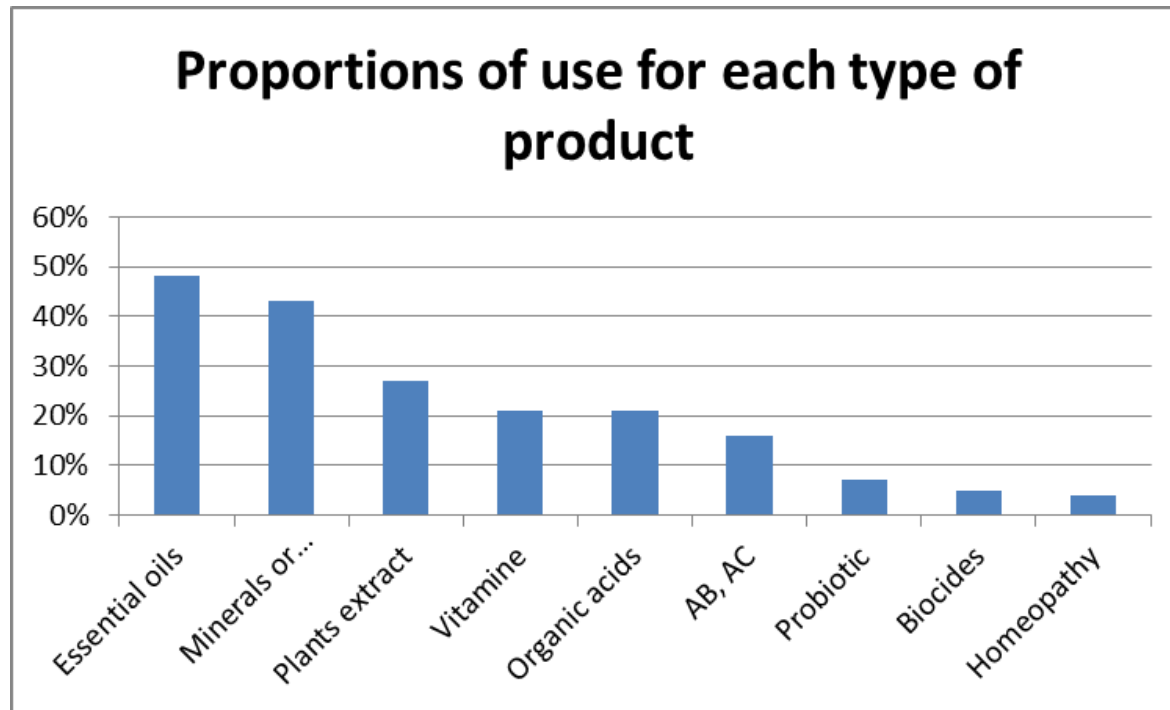
All products used were registered in one batch per farm

Results:

- 80 % of products = preventive use
- 15 batches with no product used at all
- 6 batches only used conventional products (antibiotics or anticoccidies)
- 87% of batches vaccinated against coccidies

## Use of plants and essential oils on the field

ANSES Study in organic chickens, Le Bouquin et al, 2017



## Definition of Veterinary Medicinal Product (VMP)

- any substance or combination of substances presented as having properties for treating or preventing disease in animals;
- any substance or combination of substances that may 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 to be used with a view of making a medical diagnosis;
- or to be used for euthanasia of animals



→ If a herbal product / plant extract / EO with therapeutic claim  
→ = veterinary medicine



## Example of herbal products available on the veterinary market



**COMPOSITION:** Allium Sativum, Oregano Oil, Microcrystalline Cellulose, Salts of Fatty Acids, Gelatin.

### Features of the Maycillin Bolus:

- Zero milk withdrawal
- No paperwork required
- Two boluses per cow
- Reduces SCC in cows
- No risk of contamination
- For subclinical & clinical mastitis
- Feed additive
- Bolus gun sold separately



### DESCRIPTION

Preparation for the care and prevention of udder in dairy cows.

Can be helpful with udder and teat health care and prevention

#### Properties

It prevents the teats from drying out by moisturizing and maintaining the proper pH of the skin  
Possible effect on reducing the number of microorganisms on the teat surface  
Strengthen the protective barrier of the teat canal by maintaining the integrity of the keratin litter  
Protection of the udder gland from contamination

#### Additional description

Properly combined active extracts improve the functioning of the udder gland, deeply moisturize and soften it, maintain both long-term and continuous use does not cause any skin irritation. In addition, the presence of natural factors with milking and the next thanks to the protective layer, protects the udder gland from contamination.

Description of ingredients: water extract of propolis, herbal extracts, urea



**Composition**  
Vinaigre de cidre, Macérés de rose rouge (*rosa gallica*), de thym blanc (*thymus vulgare*), de verge d'or (*solidago virga aurea*), origan (*origanum vulgare*).

**Composition**  
eucalyptol, cajeput EO, tea tree EO, nutmeg EO, cedar EO, camphor, menthol, laurel oil, colorant: chlorophylle



een one

- Several homeopathic products have a marketing authorisation and include herbal drugs.
- Few « old » veterinary chemical medicines include herbal drugs:  
For example the following products:

- . Phytophale including *Lespedeza capitata* (dry extract), Artichoke (dry extract) and Java tea (dry extract)
- . Apilife var including Thymol, Eucalyptus (oil), Camphor, Levomenthol
- . Cothivet including essential oils and tinctures

Solution for cutaneous application with Cupressis EO, Lavandulae EO, Rosmarini EO, Thymi EO, *Carlina acaulis* tincture, *Centella asiatica* tincture, Alfalfa tincture and Chestnut tincture.



## Conclusion

Herbal veterinary medicinal products are interesting alternatives to limit/reduce the use of antibiotics and the risk of antimicrobial resistance;

Already widely used in France especially essential oils, by farmers on all target species and/or prescribed by vets on pets, at least in France (and other EU MS?)

Used for treatment and/or prevention of disease, without MA, and MRL status in most of cases



## Conclusion

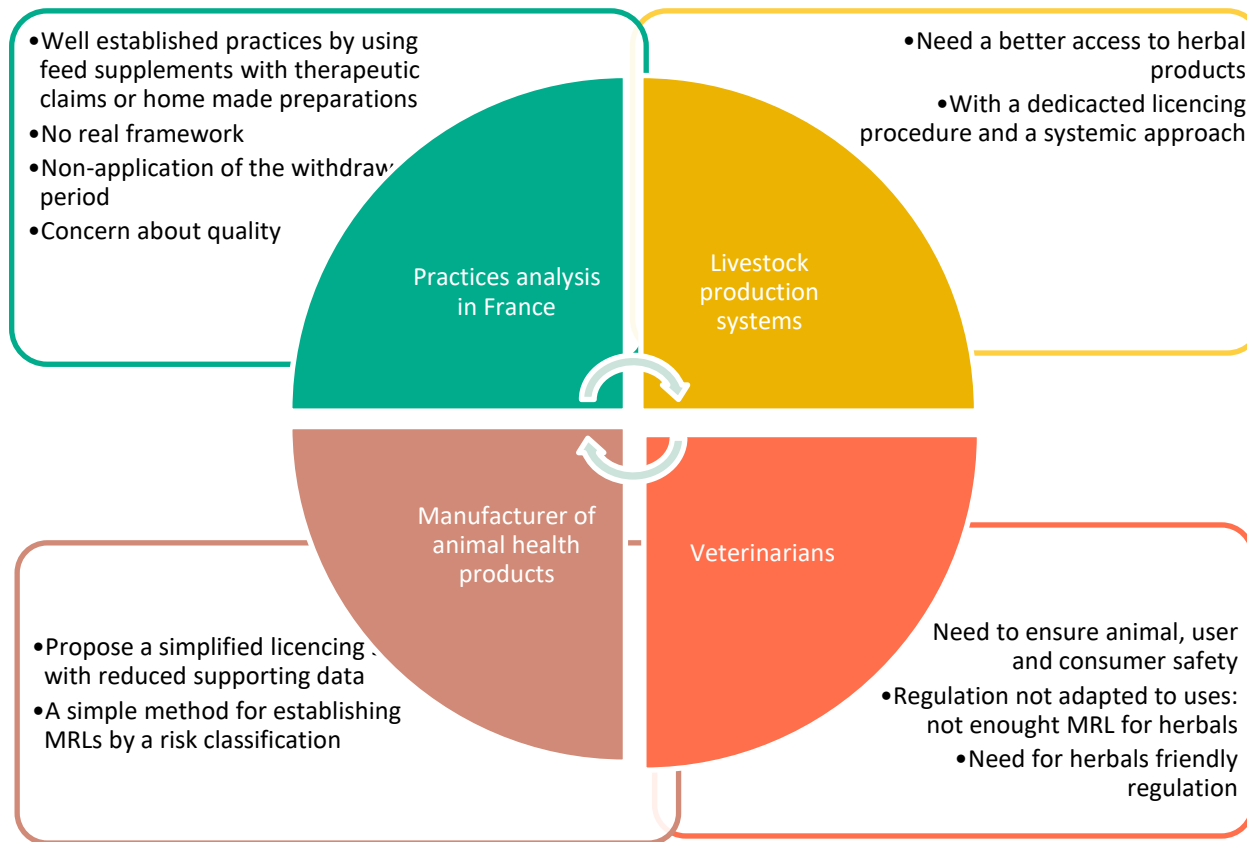
➤ **No guarantee** about quality, safety **especially consumer' safety** and efficacy

➤ **Some risks to use plants or derived plant products even if natural substances:**

- ✓ Known toxicity: for example for several essential oils as Basil oil,
- ✓ Free access of the plant / essential oils on the field :
  - No guarantee of quality: no traceability, variability of the plants, ...
  - No use of raw material for pharmaceutical use: well-controlled



# Background - Needs and proposals



## 2. Herbal Veterinary Medicinal Product – Regulatory standards for a marketing authorization

## Human side

Two possibilities in Europe for herbal medicines:

- A simple registration if the herbal drug or the herbal preparation justifies a traditional use for 30 years of which at least 15 years in the European Community, proving its safety and making its efficacy plausible (European Directive 2004/24/EC);
- A marketing authorisation if the herbal drug or herbal preparation justifies of a well-established use of 10 years in the European Community (European Directive 2001/83/EC);

## Human side

A **Committee on Herbal Medicinal Products (HMPC)** establishing EU standards to help the submission of dossiers:

Establishing **EU monographs** covering the therapeutic uses and safe conditions of well-established and/or traditional use for herbal substances and preparations :

European Union herbal monograph on *Valeriana officinalis* L., aetheroleum

Drafting a **EU list** of herbal substances, preparations and combinations for use in traditional herbal medicinal products;

Establishing **scientific guidelines** on herbal medicinal products on **quality, safety, and efficacy**



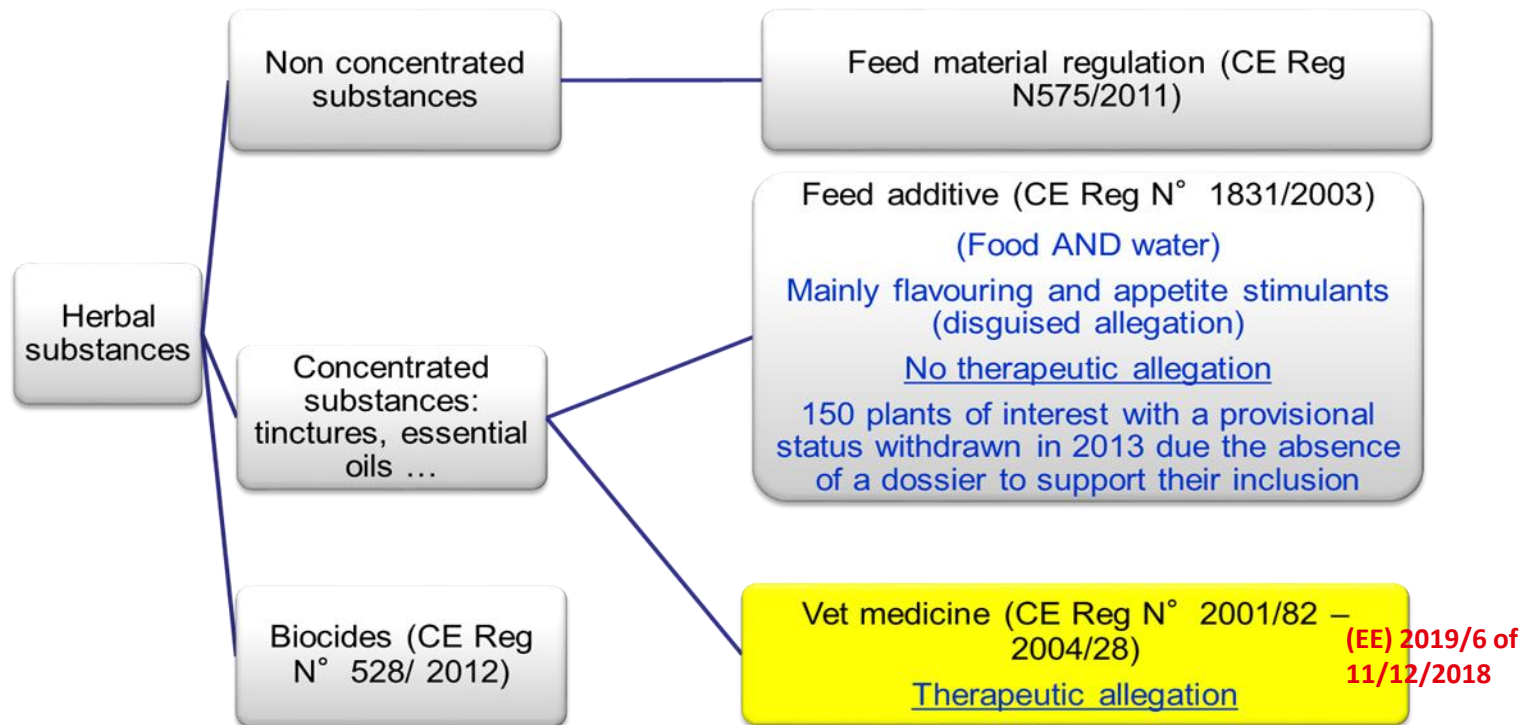
## Veterinary side

In Europe, [European Directive 2001/82/EC](#): covers [veterinary medicinal products](#), but only chemical, biological and homeopathic products.  
Well-established use is mentioned in Article 13 bis;

➡ No European reglementation for [veterinary herbal medicines](#).

- No specific scientific guidelines for these products, except for the quality part
- No specific committee on herbal products for the veterinary medicine

## Herbal substance regulatory status



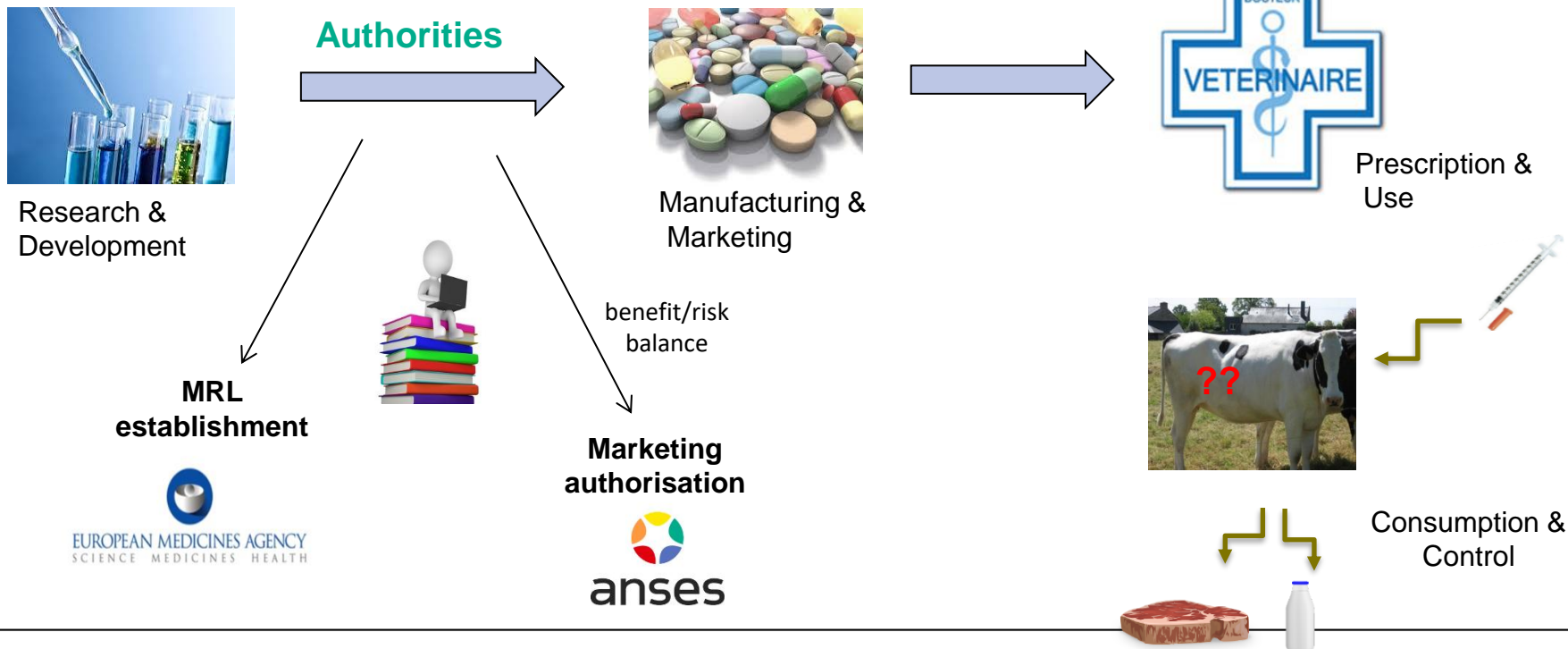
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- any substance or combination of substances that may be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;
- or to be used with a view of making a medical diagnosis;
- or to be used for euthanasia of animals



→ If a herbal product / plant extract / EO with therapeutic claim  
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## The life of a VMP



## SCIENTIFIC ASSESSMENT

## MANAGEMENT



Benefits

Risks



P  
R  
O  
P  
O  
S  
A  
L

Assessment Report

DECISION



# Dossier of marketed autorisation of pharmaceutical VMP

## Regulation (EU) 2019/6 and Commission delegated regulation (EU) 2021/805

### Part 1

- Summary of the dossier

### Part 2 : Quality documentation

- A - Product description
- B – Description of the manufacturing method
- C – Production and control of starting material
- D – Control tests carried out on isolated intermediates during the manufacturing process
- E – Control tests on the finished product
- F – Stability tests
- G – Other information

# Dossier of marketed autorisation of pharmaceutical VMP

Regulation (EU) 2019/6 and Commission delegated regulation (EU) 2021/805

## Part 3 : Safety documentation

- A – Safety tests
  - Toxicology
  - User safety
  - Environmental risk assessment
- B – Residues tests

## Part 4 : Efficacy documentation

- A - Pre-clinical studies
  - Pharmacology
  - Resistance
  - Tolerance
- B – Clinical trials

# 3 - Consumer risk assessment

## Maximum residue limit (MRL)



# Dossier of marketed autorisation of pharmaceutical VMP

Regulation (EU) 2019/6 and Commission delegated regulation (EU) 2021/805

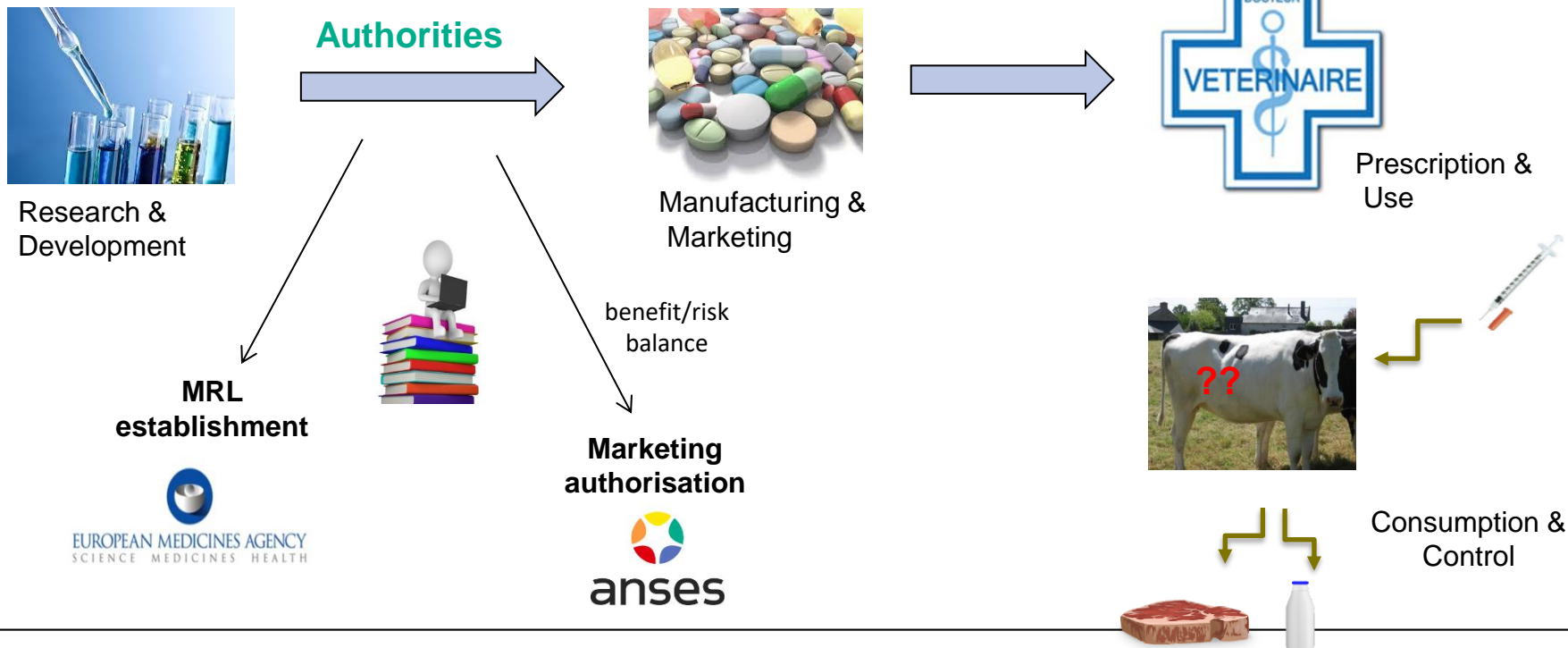
## Part 3 : Safety documentation

- A – Safety tests
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  - Environmental risk assessment
- B – Residues tests

## Part 4 : Efficacy documentation

- A - Pre-clinical studies
  - Pharmacology
  - Resistance
  - Tolerance
- B – Clinical trials

## The life of a VMP



# Maximum residue limit (MRL)

## Food safety



## Trade requirements



## European Regulations

(EC) 470/2009 of 06/05/09

(EU) 37/2010 of 22/12/09

(EU) 2017/12 of 06/01/17 (content of the application)

(EU) 2018/782 of 29/05/2018 (assessment & management)

(EU) 2017/880 of 23/05/2017 (extrapolation)

(EU) 2018/470 of 21/03/2018 (control & cascade)

(EU) 2019/2090 of 19/06/2019 (control: non compliance)

(EU) 2019/1871 of 07/11/2019 (control: reference value)

(EE) 2019/6 of 11/12/2018



## VICH Guidelines

VICH GL 36 (microbiologic ADI)

VICH GL 46 (nature of residue)

VICH GL 47 (métabolisme comparatif)

VICH GL 48 (marker residue)

VICH GL 49 (analytical method)

VICH GL 56 (honey)

VICH GL 57 (aquatic species)

## CVMP Guidelines

EMA/CVMP/516817/2009 (out of scope)

EMA/CVMP/SWP/591282/2021 (Biological substances) EMA/CVMP/SWP/90250/2010 (Biocide)

EMA/ CVMP/SWP/355698/2006 (Pharmacological ADI)

EMA/CVMP/SWP/345236/2020 (MRL Minor species)

MA/CVMP/SWP/735325/2012 (meat & offal withdrawal period)

MA/CVMP/473/98-Final (milk withdrawal period)

MA/CVMP/520191/2007-Rev.1 (injection site)

EMA/CVMP/345237/2020 (article 23)

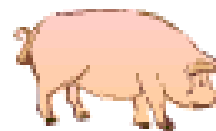
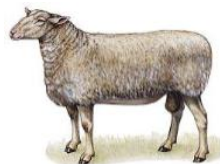
EMA/CVMP/SWP/32027/2022 (MUMS article 8)

↳ **Residues** of pharmacologically active substances means all pharmacologically active substances, expressed in mg/kg or µg/kg on a fresh weight basis, whether active substances, excipients or degradation products, and their metabolites which remain in food obtained from animals.

↳ **Food producing animals** means animals bred, raised, kept, slaughtered or harvested for the purposes of producing food.

A **MRL** is established for

- a **pharmacologically active substance**
- per **animal species**
- and per **foodstuff** of animal origin (muscle, kidney, liver, fat, milk, egg, honey)



## How is a MRL established?

### Safety part

Toxicological, Pharmacological, Microbiological data



No observed effect level (mg/kg/day)



Uncertainty factors



Acceptable daily intake ( $\mu\text{g/kg/day}$ )

### Residue part

Depletion study

Analytical method



Marker residue  
Total residue  
MR/TR Ratios  
Tissue distribution

### Management

Food basket  
Minor species  
Extrapolation  
Others uses

MRL ( $\mu\text{g/kg}$ )

# Assessment of a MRL application

According to the data provided by the applicant

- ↪ The substance is included in the **table 1** or **table 2** of the European regulation (EU) 37/2010

Table 1: **allowed substances**

- MRL value ± restriction of use
- No MRL required ± restriction of use

Table 2: **prohibited substances**

- MRL cannot be established

- ↪ Or in the **out of scope list** for pharmacologically inactive substance

# Table 1

Table 1: **allowed substances**

- MRL value  $\pm$  restriction of use
- No MRL required  $\pm$  restriction of use

Apramycin	Apramycin	Bovine	1 000 µg/kg 1 000 µg/kg 10 000 µg/kg 20 000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.	Anti-infectious agents/Antibiotics
	NOT APPLICABLE	Ovine, porcine, chicken, rabbit	No MRL required	NOT APPLICABLE	For oral use only. Not for use in animals from which milk or eggs are produced for human consumption.	



# Table 1

Substance pharmacologiquement active	Résidu marqueur	Espèce animale	LMR	Denrées cibles	Autres disposition	Classification thérapeutique
Acide clavulanique	Acide clavulanique	Bovins, porcins	200 µg/kg 100 µg/kg 100 µg/kg 400 µg/kg	Foie Graisse muscle Rein	Pour les porcins la LMR graisse concerne peau et graisse dans des proportions naturelles	Médicaments anti-infectieux /antibiotiques
		Bovins	200 µg/kg	Lait		
<i>Angelicae radix aetheroleum</i>	Non applicable	Toutes les espèces productrices d'aliments	Aucune LMR requise	Non applicable	Néant	Néant
<i>Cimifugae racemosae rhizoma</i>	Non applicable	Toutes les espèces productrices d'aliments	Aucune LMR requise	Non applicable	Ne pas utiliser chez les animaux produisant du lait destiné à la consommation humaine	Néant

## Table 2

Table 2: **prohibited substances**

- MRL cannot be established



Pharmacologically active substances	MRL
<i>Aristolochia spp</i> et l'ensemble de ses préparations	No MRL can be established
Chloramphénicol	No MRL can be established
Chlorpromazine	No MRL can be established
Colchicine	No MRL can be established
Dapsone	No MRL can be established
Diméridazole	No MRL can be established
Métronidazole	No MRL can be established
Nitrofuranes (furazolidone incluse)	No MRL can be established
Ronidazole	No MRL can be established

## Web sites

↳ EMA : summary reports & European public MRL assessment report (EPMAR)

↳ Out of scope list

<http://www.ema.europa.eu>



↳ Consolidated version of tables 1 & 2 can be found at

<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02010R0037-20160324&from=DE>

↳ Anses-ANMV: MRL values

<http://www.anses.fr>



## Rules of the veterinary drug practice: withdrawal period

⇒ For food producing animal, a VMP can be use only if the substances are included in **table 1** of 37/2010 or in « **out of scope** » list.

=> **withdrawal periods** should be determined....

# Withdrawal period

Definition according to the European regulation (EU) 2019/6:

Withdrawal period means the minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal which under normal conditions of use is necessary to ensure that **such foodstuffs do not contain residues in quantities harmful to public health.**

A **withdrawal period** is established for

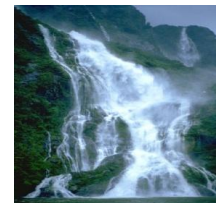
- A veterinary medicinal product
- per animal species
- and per foodstuff of animal origin (meat & offal, milk, egg, honey)

# Withdrawal period

A withdrawal period is determined

- From a depletion study : meat & offal, milk, eggs and honey
- With a validated analytical method
- By statistical or alternative approach

## Cascade use - Definitions



According to the articles 112 to 115 of the European regulation 2019/6

Use of VMP outside the terms of the marketing authorisation

Where there is no authorised VMP in a Member State for an indication concerning an animal species, the veterinarian responsible may, under his or her direct personal responsibility and in particular to avoid causing unacceptable suffering, exceptionally treat the animals concerned

Non-food-producing animal species

Antibiotic => list of not allowed antibiotics

Food-producing terrestrial animal species

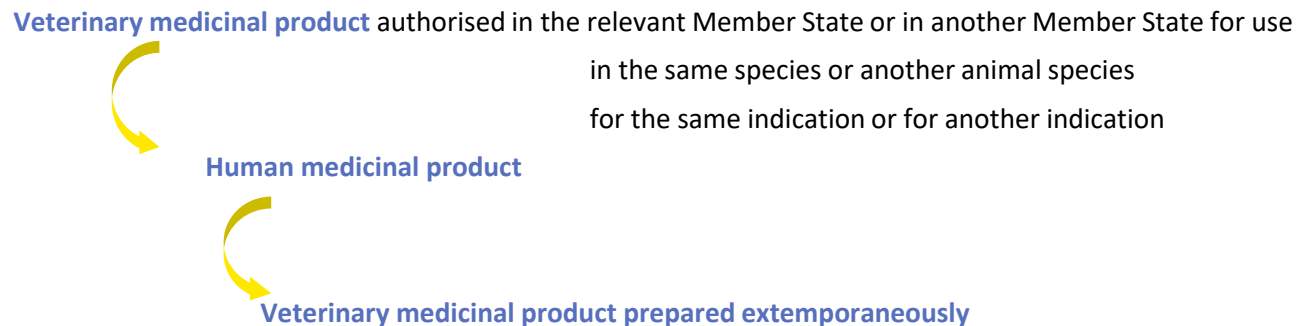
Horses => list of substances which are essential for the treatment of equine species

Food-producing aquatic species

Fish => list of allowed substances

Bees => the veterinarian shall determine the appropriate withdrawal period

## Article 112 : non-food-producing animal species



Animals of the **equine species** shall be declared as not being intended for slaughter for human consumption in the single lifetime identification document.



## Article 113 : food-producing terrestrial animal species

**Veterinary medicinal product** authorised in the relevant Member State or in another Member State for use  
in the same species or another **food-producing terrestrial** animal species  
for the same indication or for another indication

**Veterinary medicinal product** authorised in the relevant Member State for use  
in a **non-food-producing** animal species  
for the same indication

**Human medicinal product**

**Veterinary medicinal product prepared extemporaneously**

Active substance  
of Table 1

! Others  
provisions!

## Article 114 : food-producing aquatic species

**Veterinary medicinal product** authorised in the relevant Member State or in another Member State for use  
for the same indication or for another indication  
in the same species or another **food-producing aquatic** species

**Veterinary medicinal product** authorised in the relevant Member State or in another Member State for use  
in a **food-producing terrestrial animal** species

**Human medicinal product**

**Veterinary medicinal product prepared extemporaneously**

List of  
allowed  
substances

## Article 115 : withdrawal periods



### « Meat & offal » withdrawal period of food-producing mammals, poultry & farmed game birds

The longest « meat and offal » WP x 1.5

28 days if the medicinal product is not authorised for food-producing animals

1 day if the WP is zero days and is used in a different [taxonomic family](#)

### « Milk » withdrawal period



The longest « milk » WP x 1.5

7 days if the medicinal product is not authorised for animals producing milk for human consumption

1 day if the WP is zero days

## Article 115 : withdrawal periods



### « Eggs » withdrawal period



The longest « eggs » WP x 1.5

10 days if the medicinal product is not authorised for animals producing eggs for human consumption

### « Meat » withdrawal period for aquatic species



The longest WP for aquatic species x 1.5

The longest WP for food-producing terrestrial animal species x 50 (but < 500 degree.days

500 degree.days if medicinal product is not authorised for food-producing

25 degree.days if the highest WP is zero days

# 4 – Impacts on herbal veterinary medicinal products

## Promote the submission of MA applications for HVMP

### Proposed amendments

Quality section	Safety section	Efficacy section
<ul style="list-style-type: none"> <li>Possible choice of a tracer substance to ensure the quality and concentration range present in the plant drug and in the finished product.</li> <li>Possibility to provide a Pharmacopoeia certificate (as for chemical drug).</li> </ul>	<ul style="list-style-type: none"> <li>Toxicological profile: possible reference to literature, in case of old or traditional use (except for genotoxicity: at least 1 in vitro test)</li> <li>User safety minimum requirements with focus on exposure</li> <li>Tolerance: a study with finished product and if necessary restriction(s)</li> </ul>	<ul style="list-style-type: none"> <li>Possible reference to literature, for pharmacodynamic and pharmacokinetic effects (unless no data in any species or model)</li> <li>Clinical trials not required if well established use demonstrated</li> </ul>

Only 120 herbal substances of the 300 plants commonly used in food-producing animals are included in Table 1 of Regulation UE 37/2010, half of which are reserved for homeopathic or topical use

Une substance « plante » est inscrite dans le tableau 2 (usage interdit)  
*Aristolochia spp.* et l'ensemble de ses préparations

Aucune sur la liste « biological substances »

Les substances « plantes » inscrites sur la liste « out of scope » (usage autorisé) sont les suivantes

Amidon normalement trouvé dans l'alimentation et l'amidon de qualité alimentaire

*Avena (oats)*

*Carboxyméthyle* amidon sodique

Céréales

*Coffea arabica*

Huile d'olive

Huile de cacahouète = huile d'arachide

Huile de sésame

Huile de soja incluant huile de soja *époxydée*

Huile de graine de coton

Huile de maïs = huile de blé

Huile de coco

Matériel fibreux d'origine végétale

Plantes légumineuses

*Petroselinum crispum*

Soja (moulu & décortiqué)

Sciure de pin, pour abeille

*Squalane*, comme composant d'un adjuvant

Vanilline

Les substances « plantes » inscrites au tableau 1 (usage autorisé) sont présentées ci-dessous par ordre alphabétique.

Ces données sont extraites du tableau 1 publié dans le RÈGLEMENT (UE) N° 37/2010 DE LA COMMISSION du 22 décembre 2009 relatif aux substances pharmacologiquement actives et à leur classification en ce qui concerne les limites maximales de résidus dans les aliments d'origine animale.

N = 125

21 huiles essentielles

41 substances pour usage homéopathique

124 avec « aucune LMR requise » dont 1 avec une DJA

1 avec des LMR chiffrées

Angelica radix aetheroleum	Eucalypti aetheroleum
Anisi aetheroleum	Foeniculi aetheroleum
Carvi aetheroleum	Lauri folii aetheroleum
Caryophylli aetheroleum	Lavandulae aetheroleum <i>Pour usage topique uniquement</i>
Cinnamoni cassiae aetheroleum	Melissae aetheroleum
Cinnamoni ceylanici aetheroleum	Menthae arvensis aetheroleum
Citri aetheroleum	Menthae piperitae aetheroleum
Citronellae aetheroleum	Myristicae aetheroleum <i>A n'utiliser que sur l'animal nouveau-né</i>
Coriandri aetheroleum	Rosmarini aetheroleum
Cupressi aetheroleum <i>Pour usage topique uniquement</i>	Terebinthinae aetheroleum rectificatum <i>Pour usage topique uniquement</i>
	Thymi aetheroleum



The maximum allowed concentration of residue in a food product obtained from an animal that has received a veterinary medicine

Defined for a given substance, species and tissue or commodity

Aim to ensure a safe level of exposure for the consumer

European regulation on MRL			
Substances classification			
Out of scope	Biological substances	Table 1	Table 2
Not concerned by MRL = No risk	Not needing an assessment	Authorised +/- restrictions on use and/or species	Prohibited

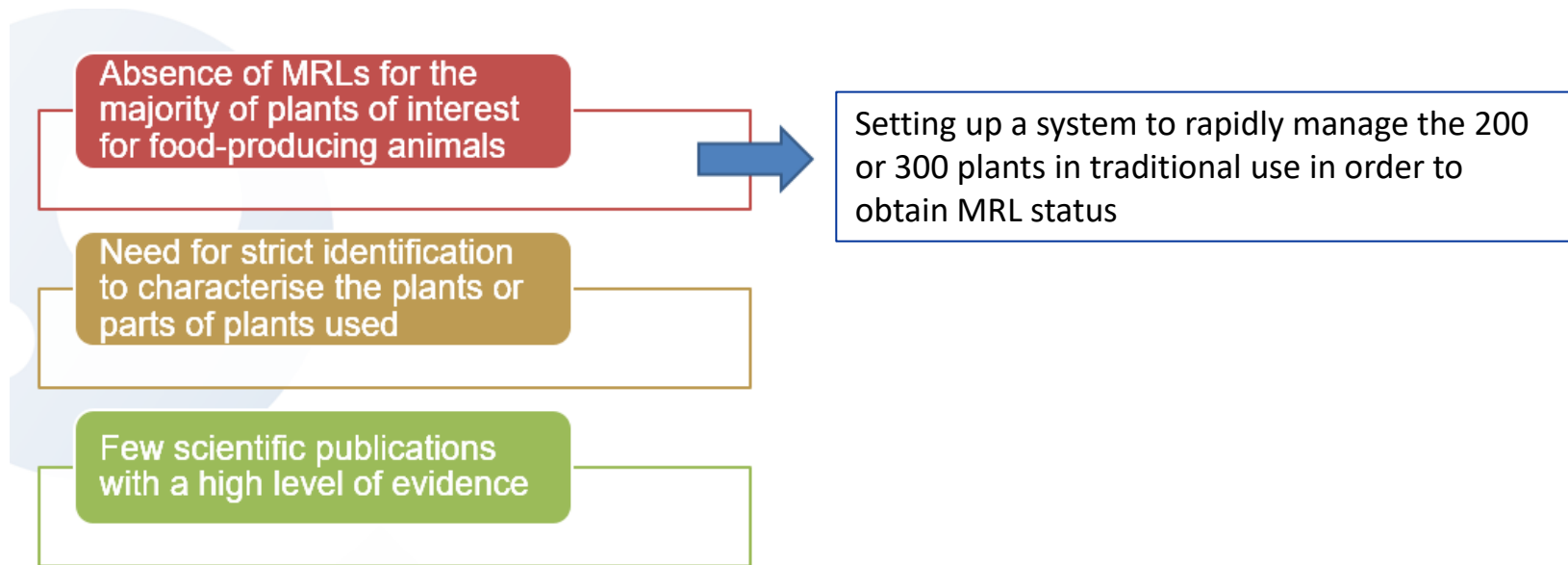
→ **Most EOs and plants currently used in VM**  
**Not listed in Table 1 or in the out of scope and biological substances lists**

Herbal specialities administered to food producing animals = complementary feedstuffs

**Reason: MRL approach not adapted to the complex and variable composition of plants, plant preparation or EOs**

## Promote the submission of MA applications for HVMP

### Major concerns



# 5. CONCLUSION



## Conclusion



- Herbal veterinary medicinal products are interesting **alternatives to limit/reduce the use of antibiotics and the risk of antimicrobial resistance**;
- Already **widely used** in France especially essential oils, by farmers on all target species and/or prescribed by vets on pets, at least in France and other EU MS and other countries,
- **Used for treatment and/or prevention of disease, without MA, and MRL status in most of cases**

## Conclusion



- **No guarantee** about quality, safety **especially consumer safety and animal safety** and efficacy

- **Some risks** to use plants or derived plant products even if natural substances:

- ✓ Known toxicity: for example for several essential oils as Basil oil,
- ✓ Free access of the plant / essential oils on the field :
  - No guarantee of quality: no traceability, variability of the plants, ...
  - No use of raw material for pharmaceutical use: well-controlled

## Conclusion



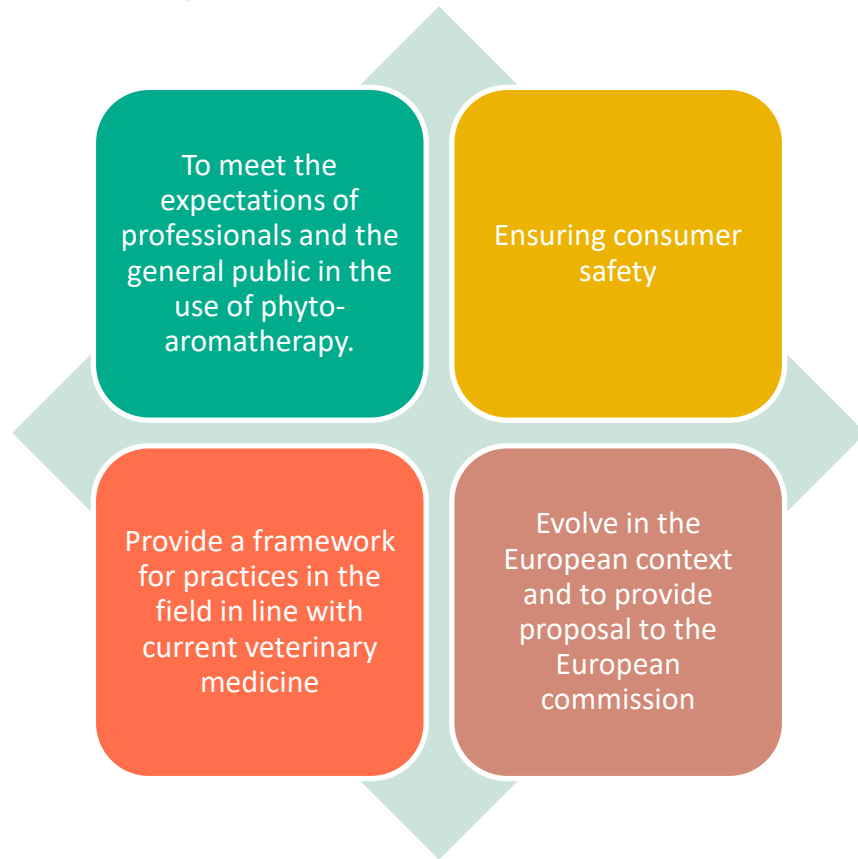
- EC encourages the use of phytotherapy for organic production but in fact there is almost no products or substances assessed and authorized neither in the feed additive list nor in our veterinary market
  - The status of this type of products should be considered in a number of cases as veterinary medicines
  - Many of plants and preparations used as vet medicines have no MRL status and **may represent a safety issue for the consumer.** (Eg: basil essential oils)
- There is a need to determine which plants and preparations can be used with no consumer safety risk → Need for MRL dossiers

## Conclusion



- To support this use, it is important **to establish MRL status** for numerous herbal substances
- The way to promote the MRL dossiers submission should always be discussed
- Always the need for **an evolution of the european regulation on veterinary herbal medicines**
- Furthermore, the **quality of the herbal drugs and herbal preparations** used on the field is also an other important point to monitor.

## As objectives





## Preamble 12:

There is **insufficient information** to date on traditional herbal products used to treat animals in order to allow the setting up of a **simplified system**. Therefore, the possibility of introducing such a simplified system should be examined by the Commission based on the information provided by the Member States on the use of such products on their territory.

## Article 157:

### **Commission report on traditional herbal products used to treat animals**

The Commission shall report to the European Parliament and to the Council by **29 January 2027**, 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**.

The Member States shall provide information to the Commission on such traditional herbal products within their territories.

# Thank you for your attention

