MedPlants 4Vet

Deliverable 9

Process description of how to generate herbal veterinary monographs

Authors

Aneliya Milanova (Faculty of Veterinary Medicine, Trakia University, Bulgaria), Anne-Marie Jacques (Anses-ANMV, France), Begum Yurdakok-Dikmen (Ankara University Faculty of Veterinary Medicine, Turkey), Carole Cousin (Anses, France), Céline Renouard (Anses, France), Chlodwig Franz (University of Veterinary Medicine Vienna, Austria), Çiğdem Bilgi (Zafer Pharmacy, Urla, İzmir, Turkey), Dezső Csupor (PharMagist Plc., Hungary), Edlira Aruci (Western Balkans University, Albania), Evelyn Wolfram (Zürich University of Applied Sciences, Institute of Chemistry and Biotechnology, Natural Products and Phytopharmacy Research Group, Switzerland), Frans Van Den Dungen (European Nutritional and Diagnostics Center, Netherlands), Jelena Arsenijević (University of Belgrade – Faculty of Pharmacy, Serbia), Laurence Millot (Adisseo, France), Liliana Vargas-Murga (University of Girona, Spain), Lise Laborieux (Anses-

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MedPlants4Vets | FiBL | Ackerstrasse 113 | Postfach 219
5070 Frick | Switzerland | Phone +41 62 865 72 72 | info.suisse@fibl.org | www.medplants4vet.eu

ANMV, France), Marta Mendel (Warsaw University of Life Sciences, Poland), Michael Walkenhorst (Research Institute of Organic Agriculture FiBL, Switzerland), Milica Drobac (University of Belgrade – Faculty of Pharmacy, Serbia), Mirjana Marčetić (University of Belgrade – Faculty of Pharmacy, Serbia), Muhammad Waqas (Ondokuz Mayis University, Turkey), Sari Koski (Finnish Medicines Agency, Finland), Theresa Schlittenlacher (Research Institute of Organic Agriculture FiBL, Switzerland)

MedPlants4Vet Deliverable No. 9 outlines in detail the methodological process for the development of herbal veterinary monographs. The primary purpose of these monographs is to present a comprehensive review of available scientific and regulatory literature concerning the use of herbal drugs and their preparations in veterinary medicine. Their primary function is to support documents for the (traditional) medicinal use of such products in veterinary practice, while also serving as reference documents that may facilitate the simplified authorization process for traditional herbal veterinary medicinal products. The process is anchored in the development of a criteria catalogue, which aims to ensure the quality, safety, and sustainability of herbal veterinary medicinal products for animal users (animal owners), consumers of food of animal origin, and the environment.

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Aneliya Milanova (Faculty of Veterinary Medicine, Trakia University, Bulgaria), Anne-Marie Jacques (Anses-ANMV, France), Begum Yurdakok-Dikmen (Ankara University Faculty of Veterinary Medicine, Turkey), Carole Cousin (Anses, France), Céline Renouard (Anses, France), Chlodwig Franz (University of Veterinary Medicine Vienna, Austria), Çiğdem Bilgi (Zafer Pharmacy, Urla, İzmir, Turkey), Dezső Csupor (PharMagist Plc., Hungary), Edlira Aruci (Western Balkans University, Albania), Evelyn Wolfram (Zürich University of Applied Sciences, Institute of Chemistry and Biotechnology, Natural Products and Phytopharmacy Research Group, Switzerland), Frans Van Den Dungen (European Nutritional and Diagnostics Center, Netherlands), Jelena Arsenijević (University of Belgrade – Faculty of Pharmacy, Serbia), Laurence Millot (Adisseo, France), Liliana Vargas-Murga (University of Girona, Spain), Lise Laborieux (Anses-ANMV, France), Marta Mendel (Warsaw University of Life Sciences, Poland), Michael Walkenhorst (Research Institute of Organic Agriculture FiBL, Switzerland), Milica Drobac (University of Belgrade – Faculty of Pharmacy, Serbia), Mirjana Marčetić (University of Belgrade – Faculty of Pharmacy, Serbia), Muhammad Waqas (Ondokuz Mayis University, Turkey), Sari Koski (Finnish Medicines Agency, Finland), Theresa Schlittenlacher (Research Institute of Organic Agriculture FiBL, Switzerland)

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1. Introduction to the herbal veterinary monograph generation process

The use of medicinal plants in veterinary medicine has long been an integral component of animal healthcare practices worldwide. Nevertheless, only a limited number of legally approved (authorized or registered) veterinary medicinal products[1] containing active substances of herbal origin remain available on the European market today. This is partly due to the absence of a simplified regulatory procedure for placing herbal veterinary medicinal products (HVMPs) on the market.

By definition, herbal medicinal products[2] contain exclusively one or more herbal drugs (herbal substances) and/or herbal drug preparations (herbal preparations) as active substances. As with all medicinal products, they must comply with established standards of quality, safety, and efficacy. Evidence supporting safety and efficacy may be derived from preclinical and clinical studies conducted during the product's development, from bibliographic sources referencing studies on the same herbal active substances (well-established use), and from scientifically documented historical or ongoing use (traditional or long-standing use).

In cases where experimental or clinical data are lacking for a particular herbal drug and its preparations, which have a long history of use in veterinary practice, evidence of safety and the plausibility of efficacy may be derived from documented traditional use. Where such documentation demonstrates sufficient safety and a plausible basis for efficacy, formal clinical tests and trials may not be strictly required, but can serve as additional supporting evidence.

Veterinary medicinal product[1] means any substance or combination of substances which fulfils at least one of the following conditions:

(a) it is presented as having properties for treating or preventing disease in animals;

(b) its purpose is 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;

(c) its purpose is to be used in animals with a view to making a medical diagnosis;

(d) its purpose is to be used for euthanasia of animals.

"Substance" means any matter of human, animal, vegetable, or chemical origin.

Herbal drugs[2] are mainly whole, fragmented, or broken plants or parts of plants, algae, fungi, and lichens, in an unprocessed state, usually in dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal drugs. Herbal drugs are precisely defined by the botanical scientific name according to the binominal system (genus, species, variety, and author).

Herbal drug preparations[2] are homogeneous products obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration, or fermentation. These include comminuted or powdered herbal drugs, extracts, essential oils, expressed juices, and processed exudates.

The purpose of a herbal veterinary monograph on a particular herbal drug and its preparations is to provide a comprehensive review of existing literature and to serve as a supporting document for its (traditional) medicinal use in veterinary practice, and

[1] *Veterinary medicinal product* as defined by Regulation (EU) 2019/6.

[2] The definitions provided for *herbal medicinal product*, *herbal drug*, and *herbal drug preparation* correspond to those set out in the European Pharmacopoeia. The terms as adopted by the European Medicines Agency (*herbal substance*, *herbal preparation*) are indicated in parentheses.

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possibly to support the simplified authorization process for the traditional HVMPs. The process of creating a herbal veterinary monograph involves thorough data collection, critical analysis and evaluation, as well as systematic reporting.

2. Monograph generation process

Writing an herbal veterinary monograph begins with a brief preliminary review to determine whether sufficient information is available to complete the process successfully. For a candidate herbal drug, the initial considerations—though not included in the final monograph—are: whether there is commercial interest (i.e., whether products containing the herbal drug and/or its preparations are available on the market and used in veterinary practice), whether a pharmacopoeia monograph exists to ensure quality, whether the herbal drug and its preparations can generally be regarded as safe, and whether there is evidence to support, or at least plausibly justify, their use in veterinary practice.

The last two points are addressed through an initial screening based on a preliminary literature review. If these questions can be answered affirmatively, a comprehensive search and evaluation of the available data can then be undertaken, culminating in the preparation of the full monograph.

2.1 Initial screening

The rationale for compiling a herbal veterinary monograph is the **known use** of the respective herbal drug and its preparations **in veterinary medicine**, together with their established recognition **as generally safe**.

The use of the herbal drug and its preparations in veterinary medicine should be supported by bibliographic references:

- Data on veterinary medicinal products available on the market (recently or in former times), brochures, etc.;
- Data on documented veterinary and historical use of herbal drugs and preparations;
- Information on Official lists of authorized/registered traditional herbal veterinary medicinal products in Member States of the European Union;
- National Pharmacopoeias of Member States used in the past, or the British Herbal Pharmacopoeia;
- Textbooks, ethnobotanical or ethnoveterinary scientific publications, etc.
- Limited additional literature search in order to get an impression of whether there are additional (recent) publications to justify their use.

The screening process for the **general safety status** of a herbal drug/preparation involves collecting data on potential toxic or adverse effects associated with the administration of the herbal drug/preparation. Such information is primarily derived from

the data on composition, experimental studies in laboratory animals, and documented use in both humans and animals. Recognition of a herbal drug/preparation as a component of food or food additive category is relevant to consumer safety in cases where food-producing animals are treated with that particular herbal drug/preparation, while its classification and use as a feed or feed additive provides safety data related to the use in target animal species. For a candidate herbal drug and its botanical source, the following regulations and lists should be checked:

- Safety data: Regulation (EU) No 37/2010 – presence in Annex Table 1 (i.e., allowed substances) with "No MRL required", the 'CPMP List of herbal drugs with serious risks', dated 1992, EFSA Compendium of Botanicals (the presence of the substances or chemical groups of concern and/or adverse effects),
- Feed and food data: Commission Regulation (EU) No 2017/1017 – Catalogue of feed materials; European Commission Food and Feed Information Portal Database (i.e. lists of feed additives as well as the lists of food additives, food allergens, food flavoring, novel foods, and nutrients); *Codex alimentarius*; Annex I of Regulation (EC) No 396/2005; Lists of plants allowed in food supplements and those not allowed for use in foodstuff (BelFrIt list, List 1 of Belgian Plants Order, Compl'Alim database status).

Additionally, the conservation status of the medicinal plant, the botanical source of the herbal drug/preparation, should be verified using the IUCN Red List, thereby providing essential data for assessing both the ecological sustainability and the ethical acceptability of plant sourcing.

2.2 Main types of data for monograph development

The herbal veterinary monograph should be based on an assessment of historical and current veterinary practices, regulatory frameworks, and published data on the quality, use, efficacy, and safety of herbal drugs and preparations in veterinary medicine. The main types of data are as follows:

- Data on the **current and historical veterinary use of herbal drug/preparation**, including data on the previous and current registered/authorized herbal products used in veterinary practice and literature data:
  - Information on the use of **veterinary medicinal products** – including herbal active substance, target animal species, indication, pharmaceutical form, posology, duration of use. Where relevant, information on other products (e.g., feed, feed additives, animal welfare products) marketed in and outside the EU/EEA may also be considered, insofar as they may provide useful context for assessing the mode of use of herbal drug/preparation in veterinary practice.
  - Special attention should be given to the evidence of efficacy and safety of use for a particular herbal drug and its preparations, which have a long-standing use. The supporting **literature data** may include:

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- **Historical books/textbooks**, i.e., publications on paper that collect the uses of medicinal plants in veterinary medical practice. This resource can be observed in its original format, manuscripts, or in a digital format. Historical publications are resources of high sociocultural value. Period of book publication should be up to 1950, having in mind medicinal, pharmaceutical, and social events (the discovery and development of penicillin and its introduction in use in the 1940s, which began the era of antibiotics, a study of Smith on the antibiotics and the nutrient requirements of the chick published in 1952, the Creation Council of Europe in 1949).
- **Systematic reviews**, including review papers, ethnoveterinary reports, PhD and master's theses (in native languages), especially those published after 1970;
- **Ethnoveterinary studies**, which are defined by McCorkle (1986) as "systematic research and development which takes as its principal subject or its major departure point folk knowledge and beliefs (theories, taxonomies, definitions, diagnoses, etc.), practices, technology and resources, social organization and so forth pertaining to any aspect(s) of animal health among species raised or managed by human beings". This includes detailed information about homemade herbal remedies (plant species, plant part, manufacturing process, source of knowledge) and the corresponding use reports (target animal species, category of use, route of administration, dosage, and further information such as source of knowledge, frequency of use, last time of use, and farmers' satisfaction).

❖ Data from the **previously published assessments and monographs** (EMA/HMPC, ESCOP, and/or WHO monographs), as well as data from European and national **pharmacopoeias** (quality data).

❖ **Other relevant publications**, including scientific publications (preclinical and clinical studies), acts of law, regulations, etc. Where possible, a comprehensive search should be undertaken and a clear research strategy should be employed and explained (e.g., PICOS scheme). This shall include simple searches with keywords, the advanced search methodology/strategy, use of additional tools (MeSH), databases (scientific, medical, toxicological, feed and food), gathering information relating to pharmacovigilance (including, e.g., UKPAR, Health Canada monographs), and other available sources.

The complete bibliography should complement the monograph.

3. Monograph structure

The structure of the monograph is based on the format of ESCOP herbal monographs and the Summary of Product Characteristics (SPC) for veterinary medicinal products, and is further adapted to reflect the specific requirements of herbal products intended for veterinary use.

The monograph is divided into three main sections:

Section 1. *Description of the herbal drug and herbal drug preparation(s)* – section describing the herbal active substance;

Section 2. *Data on veterinary medicinal use* – section containing both data on documented veterinary use and essential guidance for the proper veterinary administration of the herbal drug and its preparations (the latter corresponds to the Clinical information sections of veterinary SPC);

Section 3. *Pharmacological properties* – section describing the supporting preclinical and clinical evidence for the veterinary use of the herbal active substance proposed in the monograph.

3.1 Section 1: *Description of the herbal drug and herbal drug preparation(s)*

In this section, the description of the herbal drug and the preparations for which use is proposed should be defined as completely and accurately as possible.

3.1.1 Definition

The definition of a herbal drug includes the plant species (the name of the plant must always be given according to the binomial Latin nomenclature), the plant part(s) used, and the herbal drug description (whether dried or fresh, whole or fragmented, etc.). The definition should follow that provided in the *European Pharmacopoeia* monograph. If no such monograph exists, the use of the herbal drug should be carefully evaluated, taking into account potential quality uncertainties. If its use is accepted, the definition should be from a monograph in a national pharmacopoeia or national codex officially in use in an EU Member State, and optionally from WHO or ESCOP monographs.

Where applicable, the definition of relevant preparation(s) should be provided, following the same recommendations as for herbal drugs.

3.1.2 Constituents

The section provides a brief overview of the main active and/or characteristic compounds of the herbal drug, common qualitative and quantitative characterization, with no detailed figures or structures. If applicable (i.e., in case of documented use of specific preparation), the data on the composition of relevant herbal preparation(s) (extracts, essential oils) should be provided.

3.2 Section 2: *Data on veterinary medicinal use*

Section 2 provides guidelines for the effective and safe use of herbal drugs and their preparations in veterinary medicine based on the marketed veterinary medicinal

products and bibliographic data. It is divided into two main subsections: subsection summarizing the documented veterinary use (2.1. Overview of data on the veterinary medicinal use), and a subsection with instructions for the use of the herbal drug and its preparations in target animal species (2.2. Directions for veterinary medicinal use).

3.2.1 Overview of data on the veterinary medicinal use

This sub-section should provide the basis for the veterinary medicinal use of the herbal drug and its preparations. In this context, it provides a brief overview of the data on marketed products and the literature data (on current and historical use, and clinical trials) regarding the use of a particular herbal drug and its preparations in veterinary medicine. The collected data should be presented in such a way that they provide the full information on the proper use (herbal active substance, target species, indication, posology, duration of use).

Where appropriate, the presented data in this sub-section may be summarized in the form of a table, clearly presenting the target species, herbal drug/preparation, therapeutic area, and source of information, e.g.:

Template Table 1. Overview of documented use and clinical trials in target species

	Therapeutic areas				
Herbal drug	**TA1**	**TA2**	**TA3**	**TA4**	**TA5**
Animal Spec.1	-	HT; RES	-		
Animal Spec.2	CT	MAP_f	-		
Animal Spec.3	HT	CT	-		
Herb.prep. 1					
Animal Spec.1					
Animal Spec.2					
Animal Spec.3					
Herb.prep. 2					
Animal Spec.1					
Animal Spec.2					
Animal Spec.3					

HT: Historical Textbooks; RES: Recent Ethnoveterinary Studies; CT: clinical trials, MAP_r/MAP_f: Market authorized product (recent/former)

3.2.2 Directions for veterinary medicinal use

The subsection includes a general dosage recommendation, method of administration, and duration of use, and specific limitations for use (i.e., the following sections: target

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animal species, indications for use, dosage and route of administration, contraindications, undesirable effects), with proper referencing.

Where suitable, separate sections should be created for each target animal species.

The indications should be separated into "Internal use" and "External use", when applicable. It should be indicated whether the herbal drug/preparation is intended for (symptomatic) treatment and/or prevention. When applicable for a target animal, the indication(s) should relate to the results of clinical trials and / or the documentation cited regarding pharmacodynamic properties (Section 3).

Other information, such as special warnings, precautions for use (fertility, pregnancy, and lactation), overdose, interactions, etc., can be included here, as well as precautions to be taken by the person administering the herbal drug/preparation to animals and precautions for the protection of the environment.

For use in food-producing animals, MRL data/status may be provided.

3.3 Section 3: *Pharmacological properties*

Section 3 summarizes the relevant preclinical and clinical data on the herbal drug/preparation(s) and their constituents, supported by appropriate references to the scientific literature. This includes evidence of efficacy and safety—drawing on, but not limited to, assessments already presented in EMA/HMPC, ESCOP, and WHO monographs—and should support the use of the herbal drug/preparation described in the monograph.

3.3.1 Efficacy data

The relevant data in support of the proposed use and on the pharmacodynamic (PD) and pharmacokinetic (PK) properties (from *in vitro* studies, studies in laboratory animals, studies in healthy animals) of the herbal substance/preparation and its constituents should be presented and clearly separated. This information should, as far as possible, include details on the dosage, the plant part used, the drug-to-extract ratio, and the extraction solvent, if applicable and available, as well as the method of administration. Where available, the data from the clinical trials conducted in target (and related) animal species should be provided.

3.3.2 Safety data

Information should be given on any findings in the preclinical testing (*in vitro*, laboratory, and healthy animal studies) which could be of relevance for the safe use of the product, that is, as far as possible, data on toxicological properties of the herbal drug or herbal drug preparation and/or of the constituents, including references. The adverse reactions, potential or manifested, of herbal drug/preparation and constituents with safety concerns (e.g., estragole, thujone, etc.) should be discussed. Where available, the specific data on single and repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and

developmental toxicity, tolerance, as well as other relevant data, should be provided. Species specific differences in terms of toxicokinetics and dynamics should be discussed. In addition to pre-clinical, clinical, and regulatory safety data, when available, information from post-marketing surveillance and documented off-label use should also be considered, as these sources can provide valuable insights into rare adverse events, long-term safety, and species-specific risks.

Where available for food-producing animals, the relevant consumer safety data such as MRL, ADI, residue studies, and other findings on herbal drugs/preparations and constituents (e.g., presence of relevant plant constituents and their metabolites in milk, meat, eggs) should be provided. Where appropriate, relevant data for persons administering the herbal drug/preparation (e.g., the possibility of contact allergies) and for persons in close contact with the treated animal (e.g., owners, children, immunocompromised persons, pregnant women, etc.) should be considered. If available, data on environmental safety regarding the fate of herbal residues in manure or water, or the persistence of bioactive compounds, may be provided.

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