ANSES Opinion
Request No 2014-SA-0081

The Director-General

Maisons-Alfort, 3 February 2016

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on Request No 2014-SA-0081 – MA Veterinary phytotherapy

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It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are made public.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 3 Feb 2016 shall prevail.

ANSES-Agency for Veterinary Medicinal Products (ANMV) issued an internal request on 5 May 2014 for the following expert appraisal: No 2014-SA-0081 – MA Veterinary phytotherapy.

1. BACKGROUND AND PURPOSE OF THE REQUEST

The possibility of submitting a simplified dossier for marketing authorisation (MA) applications for veterinary medicinal products containing plants with well-established use was introduced by Decree No 2013-752 of 16 August 2013. In this procedure, the application dossier can refer to published, recognised literature on phytotherapy in traditional veterinary medical practice in France or in the European Union. Directive 2001/82/EC on the Community code relating to veterinary medicinal products does not provide for a simplified procedure specifically for herbal medicinal products. Only homeopathic products can go through this type of approval pathway under certain conditions. French legislation also provides for an MA procedure that refers to well-established use for herbal medicinal products, along with provisions for reduced fees associated with these procedures (Decree No 2015-1172 of 22 September 2015 in application of Article L. 5141-8 of the Public Health Code).

To date, only a few herbal veterinary medicinal products have been approved. In order to clarify the dossier content and expectations concerning its assessment, a working group was set up and provided details on the various parts of the MA application dossier from a scientific point of view, so as to establish recommendations on possible simplification. Enabling submission of simplified dossiers with reduced fees may encourage companies to apply for authorisation of herbal medicinal products to address the need for broader therapeutic options and growing demand for alternatives to antibiotics.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 “Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)”.

This expert appraisal falls within the area of competence of the Expert Committee (CES) on Veterinary Medicinal Products. ANSES entrusted the appraisal to the Working Group (WG) on Assessment of MA applications for herbal medicinal products. The findings were presented to the CES on Veterinary Medicinal Products concerning both methodological and scientific aspects at the following meetings: 23 September 2014, 26 November 2014, 21 January 2015, 1 April 2015 and 3 June 2015. They were adopted by the CES on Veterinary Medicinal Products during its meeting on 25 November 2015.

The report first presents the various forms of plant substances that can be used in veterinary medicine, the possible names, and the corresponding regulations and restrictions. Secondly, each part of the MA application dossier for a chemical veterinary medicinal product is discussed along with the possible simplifications for herbal veterinary medicinal products. In addition, potential extrapolations from the area of human medicine to veterinary medicine are presented. Lastly, overall recommendations with a methodology for drafting this type of dossier sum up the conclusions of the WG. A differing position is noted in the annex to the report.

ANSES analyses the relationships and interests declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert appraisal.
The experts’ declarations of interests are made public via the ANSES website (www.anses.fr).

The regulatory references and guidelines followed to carry out this expert appraisal are listed in Section 6.1.3 of the report.

3. ANALYSIS AND CONCLUSIONS OF THE CES AND WG

The WG’s findings highlighted three major points that may be obstacles to obtaining an MA for herbal medicinal products: assessment of the maximum residue limits of the substances, strict identification of the substances, and documentation on safety and efficacy. These points are discussed in detail in this opinion.

3.1. Plant substances and maximum residue limits

Maximum residue limits (MRLs) reflect acceptable levels of residue of substances contained in veterinary medicinal products, in foods sourced from treated animals.
MRLs are defined for a specific substance, species, tissue or foodstuff. They aim to guarantee an exposure level without risk for the consumer.
Assessment and classification have been carried out substance by substance since 1997 because plant substances no longer have a general status. Essential oils are also examined on a substance-by-substance basis.

Concerning the classification of pharmacologically active substances administered to food-producing animals in terms of maximum residue limits in foodstuffs of animal origin, Commission Regulation (EU) No 37/2010 contains two tables:

- Table 1 lists allowed substances (with the possibility of restrictions for use and/or species),
- Table 2 lists prohibited substances (when no MRL can be established).

After assessment by the EMA, some substances are considered to fall outside the scope of MRLs as defined in Regulation (EC) No 470/2009 and are therefore included in a list named “Out of scope” substances of the Committee for Medicinal Products for Veterinary Use (CVMP) (EMA/CVMP/519714/2009). This specifically involves substances naturally present in the body or foodstuffs entering the human diet that do not pose a risk to consumer health.
If the future veterinary medicinal product is intended for food-producing animals, the plant substance must be classified in respect of European regulations on MRLs. As a result, **the question of a plant substance’s MRL status is crucial for treatment as phytotherapy in food-producing animals, both concerning assessment of MA dossiers and prescription of products prepared extemporaneously**.

Analysis of the situation shows that only 120 plant substances listed in Annex 4 of the report, of the approximately 300 plants commonly used in food-producing animals, are included in Table 1, half of which are reserved for homeopathic or topical use. This indicates that many plant substances commonly used today in phytotherapy are not included in Table 1 and cannot at this time be included in the composition of veterinary medicinal products intended for food-producing animals or be administered to these animals as extemporaneous preparations.

Some of these plant substances may however have been authorised, including temporarily, to be included in the composition of biocidal products or animal feed.

In a context of combating antimicrobial resistance and growing interest in alternative treatment options, possibilities for treatment by phytotherapy should be enhanced to address these expectations. The development of phytotherapy for food-producing animals requires prior MRL assessment of these substances and this role falls within the competence of the EMA, which is a major obstacle for drafting an MA dossier.

The Working Group recommends establishment of a priority list of plant substances that are currently needed for phytotherapy in food-producing animals in order to encourage their assessment regarding MRL regulations, through:

- the possibility of referring to data used to comply with other regulations, particularly for biocidal products or animal feed;

- the possibility of using data from development of monographs for herbal medicinal products for human use;
- the identification of plant substances complementary to those already assessment by the EMA and that are not within the scope of MRLs and that therefore do not present a risk for consumer health;
- in the event of possible toxicity in humans, the conduct of studies on residues in collaboration with public research organisations to obtain data on tissue depletion.

As part of public policy aiming to facilitate access to herbal medicinal products, the Working Group recommends that a formal request be made to the EMA to:

- study the possibility of using plants or parts of plants when the mother tincture is included in Table 1;
- evaluate MRLs for plant substances in a general manner, irrespective of submission of MA dossiers;
- establish specific guidelines for phytotherapy veterinary medicinal products as part of work on "Herbal products", like what is done in the area of human medicine at the EMA.

Compiling an MA application dossier for a herbal veterinary medicinal product follows the same format as that used for a chemical veterinary medicinal product in the various sections, with the possible simplifications summed up below.

Part I, Administrative, non-scientific, was not dealt with in this report.

3.2. Pharmaceutical data (Quality)

Part II, Quality, is to be submitted in full with the specificities described below, because Decree No 2013-752 of 16 August 2013 does not provide for simplified pharmaceutical data.

The state of scientific knowledge when the application is made should be taken into account. All the monographs, including general monographs and general chapters of the European Pharmacopoeia, or otherwise from a Member State, are applicable.

Since the medicinal activity of the herbal drug is associated with its “totum” (total extracts), which is a complex mix of substances that are difficult to measure, the choice of the constituent or constituents used for quantification is essential when determining the quality of the herbal drug.
Since the herbal drug (plant) and/or preparation containing the herbal drug is a complex mix of constituents, it contains known and unknown constituents. In certain cases, the constituents with therapeutic activity have been identified and the known constituents are therefore quantified in the herbal drug/preparation containing the herbal drug. However, if the constituents that have therapeutic activity are not known, tracer constituents, also called analytical markers, that are representative of the herbal drug/preparation containing the herbal drug, are tested throughout the process and for the shelf-life of the active substance and finished product (if applicable).

The scientific data concerning the herbal drug/preparation containing the herbal drug or drugs are submitted either:

- using a certificate of suitability to the European Pharmacopoeia Monographs (CEP) issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM),
- using documentation specific to the MA application dossier,
- using a separate permanent dossier submitted directly to the competent authorities by the manufacturer of the active substance, also known as an Active Substance Master File (ASMF), with the active substance defined in this case as the herbal drug/preparation containing the herbal drug or drugs.

The exact scientific name of the plant is to be detailed. Given the variability in composition observed for plants, the chemotype, part of the plant, state of the plant, vegetative cycle, environment, species, and organ are important and are also to be indicated. For preparations containing herbal drug or drugs the definition of the preparation, extraction solvent, herbal drug/native extract ratio, composition, and if applicable, organoleptic/physicochemical properties, are to be presented.
Identified known constituents that have therapeutic activity, tracers (analytical markers in the case of unknown constituents) as well as the other known constituents, including toxic ones, with corresponding analytical profiles, are to be described.
It is also important to specify the following information: geographic origin, wild or cultivated state of the plant, type and period of harvest, temperature, sunshine, humidity, possible post-harvest chemical and physical treatments, as well as drying, storage and transport conditions. In the case of preparations containing the herbal drug or drugs, the method of obtaining the preparation is to be indicated and if any adjustments were made, they are to be described.

The specifications refer either to specific monographs of the European Pharmacopoeia, or to a monograph drafted by the applicant in compliance with the requirements for general monographs of the European Pharmacopoeia applicable to herbal drugs/preparations containing herbal drugs.
If appropriate, the absence of pesticide residues, heavy metals, and other contaminants is to be demonstrated.

The concentration of constituent(s) with therapeutic activity if identified, or of tracer(s), must be within the range of values accepted in the pharmacopoeia (if applicable), to ensure consistent quality of the herbal drug.

Considering the complexity and variability of composition observed for plants and therefore the potential variability in safety, toxicity and efficacy, identification of the plant, its full characterisation, testing of known therapeutically active constituents or testing of tracers, as well as comparison of the analytical phytochemical profiles, such as chromatographic profiles, are essential and are to be described in detail to ensure consistent quality of the source herbal drug (plant) and/or preparation containing the herbal drug or drugs.

Concerning testing of the herbal medicinal product, it is important to combine several methods to clearly identify the plant and ensure a correlation between the phytochemical profile of the finished product and that of the plant and/or herbal preparation on release and during stability testing.

For stability, the possible period of retesting before manufacture is to be indicated for the herbal drug, and where applicable for the preparation containing the herbal drug. In addition, in the case

of a preparation containing herbal drugs, the stability of other constituents and the maintenance of their proportions is also to be studied.

If a herbal medicinal product contains several herbal drugs or preparations containing a herbal drug or drugs and if it is not possible to determine the stability of each active substance, the stability of the medicinal product must be determined using chromatographic methods, by physical testing, and/or by overall assay methods, or any other suitable assay.

It is essential to establish the link between the quality part and data from the literature on efficacy as well as any toxicology studies carried out, particularly to ensure that the bibliographic references and the studies relate to the same plant or plants, or parts of plants.

3.3. Safety tests and residue studies

Part III, on **Safety** of the medicinal product and residue studies should be submitted with the specificities indicated below.

3.3.1. Toxicology

The requirements for chemical veterinary medicinal products and those for human use containing plants serve as a basis in this report to establish recommendations on **toxicology** for herbal veterinary medicinal products.

In summary, the following points must be maintained:

- for the genotoxicity assessment, i.e. induction of physical or functional changes in the genome, data on mutagenicity, i.e. ability to cause genetic mutations, must be obtained using studies conducted as per GLP[1] and in compliance with OECD[2] guidelines; any form of literature support data can be analysed for toxicity requirements (single-dose and/or repeated-dose toxicity, specific toxicity such as irritation or sensitisation, or reprotoxicity) and for carcinogenesis requirements; plant substances for which a monograph has already been established in human medicine are likely to satisfy these requirements;

- for the tolerability assessment, it is possible not to perform a study but to rely on literature data, only if they are available for the target species;

- it is necessary to assess the possibility of interactions with other medicinal products and/or other substances.

It is therefore possible, with the exception of considerations concerning mutagenicity, that most of the data on toxicity can be obtained from information related to well-established use, i.e. bibliographic data from scientific literature specific to veterinary phytotherapy and traditional veterinary medicine, provided that the data are of high quality, as well as information on tolerability, but only if it is available in the target species.

[1] Good laboratory practice
[2] Organisation for Economic Cooperation and Development

For the assessment of genotoxicity, the contribution of exposure to the medicinal product should be considered in terms of usual human and animal exposures. This requires at least a bacterial reverse mutation test, known as an Ames test, and that the corresponding results be documented in the application dossier. The results of this test determine the need for other more in-depth tests on genotoxicity or even carcinogenesis. In the absence of suspected carcinogenicity, corresponding tests are not required unless chronic administration is being considered, or if the absence of mutagenic potential has not been demonstrated, or if there is structural analogy between one of the constituents and a known carcinogen.

Reprotoxicity studies are not required unless there are known effects during gestation or if the medicinal product is likely to be administered during gestation or lactation. In the absence of data, the medicinal product will be contra-indicated in gestation and/or lactation.

An expert assessment should also examine whether the presented data belong to plant species of the same genus or the same family as the plant substance of interest. In the case of a herbal drug (plant) and/or a herbal preparation, the tested samples should be representative of all the herbal preparations belonging to the same phytochemical profile.

Depending on the quality of the available data, many types of studies are therefore not required. It is however necessary to justify use of literature data in a different species to the target species.

3.3.2. Safety of the user

Concerning assessment of the **safety for the user**, the principle behind the assessment involves a three-step approach: characterisation of the hazard (toxicity data), assessment of exposure (people and circumstances, before, during and after administration) and characterisation of the risk involved. Depending on the type of toxicity considered, the dose-response relationship should be established to determine the no observed effect level, or if this is not possible, the lowest dose at which effects are observed. Analysis of exposure make it possible to answer the following five questions: who, how, what, when, how much, and at what frequency? It should include an assessment of the notions of local toxicity and associated risks. Characterisation of the risk should be qualitative and/or quantitative.

If necessary, management measures should be proposed to make the risk acceptable. These management measures will be accompanied by risk information measures.

3.3.3. Environmental risk

An assessment of the **environmental risk** should be carried out according to VICH[3] GL6 and GL38 guidelines.

In view of the nature of the product in question, i.e. a natural substance that when used will not affect the concentration or distribution of the substance in the environment, assessment of the risk for the environment should generally be limited to a phase I assessment (see decision tree in the VICH GL6 guideline). In application of this guideline, most of the products used in phytotherapy will not require a specific study.

[3] Veterinary International Conference on Harmonization

However, for certain plants, for example those that have endocrine disruptor properties, a case-by-case analysis should be performed.

3.3.4.Evaluation of residues

Concerning **residues**, determining the withdrawal period by a residue depletion study for a herbal veterinary medicinal product remains essential when the target species are food-producing animals. A withdrawal period must therefore always be defined based on MRLs for the various constituents of the medicinal product. It is possible in the dossier to refer to the European public MRL assessment report (EPMAR) or to make use of existing World Health Organization (WHO) monographs and scientific publications. In the case of several active substances, the longest withdrawal period should be retained for the medicinal product.

The Working Group recommends that the proposed regulation on veterinary medicinal products should determine the conditions that make it possible to define fixed withdrawal periods of zero days for substances that do not require an MRL.

3.4. Efficacy

Part IV, Efficacy of the product, is to be submitted with the specificities described below.

Concerning the preclinical part, the pharmacodynamic effects, mechanisms of action and pharmacokinetics, as well as data available in the literature, should be described, irrespective of the study model. Studies in the target species are not essential and a summary based on inter-species extrapolations can be considered, including on the basis of results in humans.

The issue of potential development of resistance for substances with antibacterial or antiparasitic activity should be discussed and evaluated.

Tolerability in the target animal should be studied in terms of possible local and systemic effects, with no simplification possible.

A summary of the literature data can be used to document well-established use and justify an indication, substantiating the clinical part. Nonetheless, if full efficacy is not demonstrated, the target indications will need to be in line with the level of evidence provided. Given that the benefit of these medicinal products may not be clearly established, i.e. unproven efficacy, it will be necessary to show that they have good tolerability.

The Working Group carried out literature searches on three examples and found a small number of references in peer-review journals and more references in “grey literature”. The Working Group recommends use of a qualification methodology of the level of evidence using an analysis grid. Each article can thus be evaluated on the basis of how it fits into the defined framework and of the following three points:

- suitability of the study protocol to the question posed,
- presence or absence of major bias in study conduct, including the statistical analysis by the authors, and the study’s power.

- use of the grading system, for example using the ANAES[4] scale proposed by the WG: A for established scientific proof, B for scientific assumptions, and C for a low level of evidence. These levels of evidence would be described in the SPC for the herbal medicinal product.

[4] French National Health Assessment and Accreditation Agency

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the WG examined each section of the MA application dossier in order to specify acceptable simplifications. It arrived at the following conclusions:

- indicating a withdrawal period remains essential for medicinal products intended for production animals and prior submission of an MRL assessment request to the EMA may be necessary, which constitutes a limiting factor. The mandatory nature of the MRL status and the limited number of active plant substances included in Table 1 and in the “out of scope” list of Regulation (EC) No 37/2010 result in the need for implementation of a system that enables rapid management of the 200 to 300 traditionally used plants so that they can obtain a specific MRL status;
- strict botanical identification should be specified, taking into account possible variations in composition; use of a tracer can be considered and the suitability of its characterisation with the requirements of the European Pharmacopoeia then becomes necessary;
- with the exception of particulars concerning mutagenicity, most toxicity data can be obtained from data related to well-established use;
- preclinical data can be obtained from the literature with the possibility of inter-species extrapolation, since data in the target species are only required in terms of tolerability;
- clinical data can come from the literature with a critical analysis and summary of their admissibility in terms of scientifically acceptable levels of evidence.

The Working Group recommends establishing a list of plant substances that are currently needed for phytotherapy in food-producing animals in order to encourage assessment regarding MRL regulations, through:

- the possibility of referring to data used to comply with other regulations, particularly for biocidal products or animal feed;
- the possibility of using data from development of monographs for herbal medicinal products for human use;
- the identification of plant substances complementary to those already assessed by the EMA and that are not within the scope of MRLs (“Out of scope” list) and that therefore do not present a risk for consumer health;
- in the event of possible toxicity in humans, the conduct of studies on residues in collaboration with public research organisations, in order to obtain data on tissue depletion.

As part of public policy aiming to facilitate access to herbal medicinal products, the Working Group recommends that a formal request be made to the EMA to:

- study the possibility of using plants or parts of plants when the mother tincture is included in Table 1;
- evaluate MRLs for plant substances in a general manner, irrespective of submission of MA dossiers;
- establish specific guidelines for phytotherapy veterinary medicinal products as part of work on "Herbal products", like what is done in the area of human medicine at the EMA.

The Working Group recommends that the proposed regulation on veterinary medicinal products should determine the conditions that make it possible to define fixed withdrawal periods of zero days for substances that do not require an MRL.

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions of the WG:

- MRL assessment of herbal substances is a major obstacle to development of MA dossiers for herbal medicinal products,
- strict identification of the substances remains crucial,
- use of literature data can follow a qualification methodology of levels of evidence using an analysis grid in order to document efficacy and safety, with the exception of data concerning mutagenicity and a tolerability study in the target species.

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KEY WORDS

Plants, parts of plants, plant secretions, extraction substances, use in veterinary medicine