The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CALENDULA OFFICINALIS
(use in veterinary homeopathy)

SUMMARY REPORT

1. *Calendula officinalis* (synonym: common marygold) is a plant of the family *Asteraceae.* The dried ligulate florets, the dried composite flowers of *Calendula officinalis* (*Calendulae flos)* and the dried aerial parts of *Calendula officinalis* (*Calendulae herba)* collected during the flowering period are used in medicinal products. The homeopathic mother tincture for use in veterinary medicine is prepared according to homeopathic pharmacopoeias by ethanolic extraction of the fresh flowering aerial parts of *Calendula officinalis.*

   Constituents of *Calendulae flos* include flavonoids (0.3 to 0.8%) such as flavonols (isorhamnetin, quercetin) and flavonol glycosides including isoquercitrin, narcissin, neoliesperoside and rutin; volatile oil (0.2%) with sesquiterpenes, such as α-cadinol (27% of the oil) and δ-cadinol (13% of the oil) as main components and also containing menthone, isomenthone, caryophyllene, pedunculatine, (α and β-ionone, a β-ionone epoxide derivative, dihydroactinidiolide; triterpenoids, such as saponins with oleanolic acid as an aglycone (i.e. glycosides A to F, 2 to 10% of dry weight), and a large number of acylated pentacyclic mono-, di-, and tri-hydroxy-triterpenes derived from Ψ-taraxen, taraxen, lupen, oleanen and ursen, with the triterpene alcohols occur both in free form and as esters; sterols (0.06 to 0.08%), present as free alcohols, esters and glycosides; coumarins such as scopoletin, umbelliferon and aesculetin, carotenoids in form of a large number of carotene- and xantophyll-derivatives, and polysaccharides, 14.8% water-soluble polysaccharides consisting of acidic, branched heteroglycanes (rhamno-arabino-galactanes and arabino-galactanes). No further constituents have been reported for *Calendulae herba.* Therefore the information available on the toxicity of *Calendulae flos* is also considered to be relevant to the assessment of veterinary homeopathic preparations of *Calendula officinalis*.

   The Committee for Veterinary Medicinal Products (CVMP) previously assessed *Calendulae flos* in respect to its use in veterinary phytotherapy and recommended its inclusion in Annex II of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Animal species	Other provisions
Calendulae flos	All food producing species	For topical use only

2. This application relates to the homeopathic mother tincture of *Calendula officinalis,* which is intended for use in all food-producing animals. The use follows the principles of homeopathic therapy where animals are diagnosed on basis of the individual pattern of clinical signs. The recommended maximum parenteral dose for large animals is 10 ml/animal. Treatment may be repeated but a fixed dose schedule is not common in homeopathy.

   Calendula officinalis is also used in human homeopathy as the mother tincture as well as in lower concentrations.

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3. *Calendulae flos* preparations are of moderate acute toxicity. The intravenous and intraperitoneal LD_{50} in mice of aqueous extracts is reported to be 300 to 375 mg/kg bw. For an aqueous-ethanolic extract (30% ethanol) the LD_{50} is reported to be 45 mg/mouse, subcutaneously and for the rat it was reported to be 5260 mg/kg bw, intravenously. No toxic symptoms were observed in the hamster orally given 0.15 g/kg bw/day for a period of 18 months of an extract of *Calendulae flos* (solvent not reported).

4. The above Annex II recommendation for *Calendulae flos* is considered to also cover the topical use of veterinary homeopathic preparations of *Calendula officinalis* in all concentrations, including the mother tincture.

   The use of *Calendula officinalis* in veterinary homeopathy was further considered in a preliminary risk evaluation procedure by the Committee for Veterinary Medicinal Products, considering all defended old substances used in veterinary homeopathy in concentrations greater than 1:10 000. Apart from the acute toxicity, further information made available and systematic search of published literature did not provide any further evidence for pharmacological or toxicological properties of *Calendula officinalis* and its constituents alerting to specific health risks, which may result from residues in food producing animals following the intended uses. Special emphasis was put on identification of suspicion pointing to genotoxicity or other potential of serious health effects of plant constituents. It was concluded, that for all other routes of administration homeopathic dilutions of *Calendula officinalis* resulting in concentrations in the veterinary medicinal product not exceeding 1 part per 10 may be used, as they can be considered as not giving rise to any specific consumer health concerns and provide a sufficient margin of safety.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- *Calendulae flos* for topical use has already been included in Annex II of Council Regulation (EEC) No 2377/90,
- *Calendula officinalis* is used in a small number of individual animals for non-regular treatments,
- animals are unlikely to be sent for slaughter during or immediately after treatment,
- *Calendula officinalis* constituents did not give rise to specific consumer health concern which may result from veterinary homeopathic uses in food producing animals;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Calendula officinalis* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Animal species	Other provisions
Calendula officinalis	All food producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations in the products not exceeding one part per ten only