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EMA/CVMP/519714/2009
Committee for Medicinal Products for Veterinary Use

Substances considered as not falling within the scope of Regulation (EC) No. 470/2009², with regard to residues of veterinary medicinal products in foodstuffs of animal origin

1. Background information

Regulation (EC) No. 470/2009 lays down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin. The Regulation repealed Council Regulation (EEC) No. 2377/90.

Article 1(1)(a) of Regulation (EC) No. 470/2009 defines its scope as follows:

“For the purposes of ensuring food safety, this Regulation lays down rules and procedures in order to establish:

- a) the maximum concentration of a residue of a pharmacologically active substance which may be permitted in food of animal origin (maximum residue limit);
(...)”

Article 1(2)(a) of the above-referred Regulation states that:

“This Regulation shall not apply:

- a) to 'active principles of biological origin intended to produce active or passive immunity or to diagnose a state of immunity, used in immunological veterinary medicinal products'.”

In Article 2(a) it is specified that “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.

Previously, in the context of the evaluation of MRL applications under Council Regulation (EC) No. 2377/90, the CVMP discussed the concept of “pharmacologically active substances”, in particular considering the need for MRL evaluations for excipients and manufacturing materials. As detailed in the CVMP publication entitled *Position Paper on the definition of substances capable of pharmacological action in the context of Directive 2001/82/EC, as amended, with a particular reference to excipients*

¹ Rev.49: Formatting of the heading Chemically complex substances of natural origin

² Regulation (EC) No. 470/2009 of the European Parliament and of the Council of 6 May 2009, repealing Council Regulation (EEC) No. 2377/90



and manufacturing materials (EMEA/CVMP/072/97-Rev.13), it was concluded that "substances capable of pharmacological action are substances pharmacodynamically active at the dose at which they are administered to the target animal by means of the veterinary medicinal product in which they are included". It follows that if an excipient has not pharmacodynamically activity at the relevant dose, then no MRL evaluation would be needed.

Subsequently, the Committee adopted a paper entitled *Reflection Paper on consideration of adjuvants and preservatives under Council Regulation (EEC) No. 2377/90 laying down a community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin* (EMEA/CVMP/339116/2007-CONSULTATION), in which it is concluded that the approach used to determine whether an MRL evaluation is required for preservatives and adjuvants should be the same as is used in relation to excipients (i.e. it should be based on the presence or absence of pharmacodynamic activity at the intended dose).

Since the implementation of Council Regulation (EEC) No. 2377/90, the CVMP has deliberated on many substances (including excipients, adjuvants and preservatives) to be used in veterinary medicinal products intended for food producing species, and regularly receives requests (either scientific advice or ad hoc requests) to consider whether such substances fall within the scope of the MRL regulation. The substances for which the CVMP has concluded that no MRL evaluation is required are listed in the CVMP publication "Substances considered as not falling within the scope of Regulation (EEC) No. 2377/90" (EMEA/CVMP/046-00), also often referred to as the 'out of scope list'.

The list also includes a small number of compounds that do not fall within the categories of excipients, adjuvants or preservatives but are natural substances essential for life or are biologically active constituents. Due to the nature of these specific compounds the CVMP considered that an evaluation for the establishment of maximum residue limits would not be appropriate.

Following the implementation of Regulation (EC) No. 470/2009 there was a need to update the background information and legal references included in the document containing the 'out of scope list'. This document performs that function and supersedes the CVMP publication *Substances considered as not falling within the scope of Council Regulation (EEC) No. 2377/90*. The list presented on the following pages includes all the substances included in the superseded document.

It should be noted that this list of substances is in no way exhaustive and includes only substances for which requests in this respect were made to CVMP by a company or a national authority.

Any enquiries may be sent to mrl@ema.europa.eu

³ Initially adopted in April 1997 and further revised in July 2004

2. Substances considered as not falling within the scope of Regulation (EC) No 470/2009

Excipients

Acetone (CAS No: 67-64-1): for cutaneous use only

Alcohols, C9-11, ethoxylated (CAS 68439-46-3)

Aqua purificata (CAS No: 7732-18-5)

Bentonite (CAS No: 1302-78-9): for cutaneous and oral use only

Benzethonium chloride (CAS 121-54-0): for use as a preservative at concentrations of up to 0.01% resulting in target animal doses of up to 8 µg/kg bw

1,2-Benzisothiazol-3(2H)-one (CAS No 2634-33-5): for cutaneous use only

Bis(2,6-diisopropylphenyl)carbodiimide (CAS No: 2162-74-5): for cutaneous or in-hive use only

2-(2-n-Butoxyethoxy) ethanol (CAS No: 112-34-5)

Carbomer (CAS No: 9003-01-4)

Carbomer copolymer A (CAS No: 1456857-02-1): for topical administration at doses of up to 1.6 mg/kg bw

Casein hydrolysate (CAS No: 65072-00-6)

Cetearyl ethylhexanoate (CAS No: 59130-70-7): for cutaneous use only at doses of up to 35.0 mg/kg bw

Chlorobutanol (CAS No: 57-15-8): at concentrations up to 1%

Coconut oil (CAS No: 8001-31-8)

Collagen hydrolysate (CAS No: 9007-34-5)

Copolymer of polyvinylpyrrolidone and vinyl acetate (CAS No: 25086-89-9): for cutaneous use only

Corn oil (CAS No: 8001-30-7)

Cotton seed oil (CAS No: 8001-29-4)

Cytosine-phosphate-guanine 23877: for use as an adjuvant at concentrations of up to 100 µg per dose

Denatonium benzoate (CAS No: 3734-33-6): for topical administration at doses of up to 0.25 mg/kg bw

N-(2-deoxy-2-L-leucylamino-β-D-glucopyranosyl)-N-octadecyl-dodecanoylamide hydroacetate: for use as an adjuvant at concentrations of up to 1 mg per dose

Didodecyl 3,3'-sulfanediylidipropanoate (CAS No: 693-36-7): for in-hive use only

Diethylaminoethyl (DEAE)-dextran (CAS No: 9015-73-0) and diethylaminoethyl (DEAE)-dextran hydrochloride (CAS No: 9064-91-9): at concentrations up to 150 mg/ml

Diethylhexyladipate (DEHA) (CAS No: 103-23-1): for cutaneous use only at doses of up to 45 mg/kg bw

Dimethyldioctadecylammonium bromide (CAS No: 3700-67-2): for use as an adjuvant at a total dose of not greater than 21 mg/animal.

Dimethyl ether (CAS No: 115-10-6): for use as a propellant for topical administration

di-n-butyl-adipate (CAS No: 105-99-7)

Di-polyethylene glycol-6 ester of oleic acid (CAS No: 879124-92-2): at doses of up to 1 mg/kg bw

Dipropylene glycol (CAS No 106-62-7, 110-98-5, 108-61-2 and 25265-71-8): for cutaneous use only

Dipropylene glycol methyl ether (CAS No: 34590-94-8)

2-[2-(dodecyloxy)ethoxy]ethanol (CAS No: 3055-93-4): for cutaneous use only

Dolomite (CAS No: 16389-88-1)

Erucamide (CAS No: 112-84-5): for in-hive use only

Ethoxylated nonylphenol with an average of 9–10 ethylene oxide moieties (generic CAS No: 9016-45-9): at a total dose not greater than 1 mg per animal

Ethoxylated octylphenol with an average of 7–9 ethylene oxide moieties (generic CAS No: 9036-19-5): at a total dose not greater than 1 mg per animal

Ethoxyquin (CAS No: 91-53-2): at concentrations up to 0.1 mg/g

N-Ethylglucamine (CAS No 14216-22-9)

Fatty acid methyl esters (CAS No: 67762-38-3): for topical administration

Fibrous materials of plant origin

Gamma hexalactone (CAS No: 685-06-7): for topical administration at doses of up to 14 mg/kg bw

Gelatin (CAS No: 9000-70-8)

Glycerol dimethylketal (CAS No: 100-79-8): at concentrations up to 150 mg/ml

Natural crystalline graphite (CAS No: 7782-42-5): for use as anionic material in intraruminal devices

4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (CAS No: 7365-45-9): for use as a buffering agent in vaccines and vaccine diluents

Isopropyl myristate (CAS No: 110-27-0): at doses up to 5 mg/kg bw

Isotridecanol ethoxylates (CAS no. 69011-36-5)

Macrogol cetostearyl ether (CAS No: 68439-49-6): for administration by the intramammary route at doses of up to 0.95 mg/kg bw

Maleic acid (CAS No: 110-16-7): for use in buffering systems at doses up to 0.39 mg/kg bw

Meglumine (CAS No: 6284-40-8): at doses up to 1.5 mg/kg bw

Metacresol (CAS No: 108-39-4): at concentrations up to 0.2%

Methacrylic acid - ethyl acrylate copolymer (CAS No 25212-88-8): for oral use only

Monophosphoryl lipid A (CAS No 1246298-63-4): for use as an adjuvant at concentrations of up to 6 µg per dose

Nonwoven polyester fabric consisting of fibres made of polyethylene terephthalate (CAS No: 25038-59-9) and polyethylene terephthalate copolymer (isophthalic acid terephthalic acid ethylene glycol polymer; CAS No 24938-04-3): for cutaneous use only

Octadecenoyloxyethyl-heptadecenyl-hydroxyethylimidazolium chloride (DOTIM) (CAS: 214909-22-5): for intramuscular use as part of a vector for immunostimulants at doses up to 356 µg/animal

2-Octyl-dodecanol (CAS No: 5333-42-6): when administered topically at doses up to 20 mg/kg bw

Oleic acid (CAS No: 112-80-1)

Olive oil (CAS No: 8001-25-0)

Peanut oil (CAS No: 8002-03-7)

Pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (CAS No: 6683-19-8): for in-hive use only

Phosphodiester oligodeoxynucleotides: for use as adjuvant

Pine wood flour: for in-hive use only

Polybutene (CAS No: 9003-29-6)

Polydimethylsiloxane, dimethylvinyl-terminated (CAS No: 68083-19-2): for in-hive use only

Polydimethylsiloxane, hydroxy-terminated (CAS No 70131-67-8): for cutaneous use only

Polyethylene (CAS No: 9002-88-4): for cutaneous use only

Polyethylene glycol-8 beeswax

Polyethylene glycol-75 lanolin (CAS no 8039-09-6 and 61790-81-8): for topical use only

Poly(ethylene-vinyl acetate) (CAS No: 24937-78-8)

Poly(lactic-co-glycolic acid)

Polysaccharides naturally occurring such as celluloses and hydroxycelluloses, dextrans and glucans

Polymyxin B (CAS No: 1404-26-8): for use as an endotoxin neutralising agent in vaccines at doses of not more than 500 µg/dose (approximately 5000 IU per dose) or not more than 8 µg/kg bw (approximately 80 IU/kg bw), whichever is the lower

Polyvinyl chloride homopolymer (PVC) (CAS No: 9002-86-2), with a vinyl chloride limit < 1 ppm

Polyoxyethylene cetyl ethers (ceteths, CAS No 9004-95-9): at doses up to 1 mg/kg bw

Polyoxyethylene (9) lauryl ether (CAS No: 3055-99-0): for cutaneous use only

Polyoxyethylene oleate (CAS No. 9004-96-0): at doses up to 1.15 mg/kg bw

Polyoxyethylene oleic alcohol (CAS No 9004-98-2): at doses up to 0.95 mg/kg bw

Polyoxyethylene (40) sorbitol septaoleate (CAS No: 63089-85-0): for cutaneous use only

Polyoxypropylene (PPG-2) myristyl ether propionate (CAS No: 74775-06-7): for cutaneous use only

Polypropylene (CAS No: 9003-07-0)

Propolis

Propylene carbonate (CAS No: 108-32-7): at doses up to 16 mg/kg bw when applied by injection and with no dose restriction when administered cutaneously or orally⁴

Sesame oil (CAS No: 8008-74-0)

Silicones (CAS No: 9006-65-9)

Simethicone (CAS No: 8050-81-5)

Sodium lauryl ether sulfate (CAS No 68891-38-3): for cutaneous use only

Sodium polynaphthalene sulfonate (CAS No 9084-06-4): for cutaneous use only

Sodium starch glycolate (CAS: 9063-38-1): for oral and cutaneous use only

Soybean (milled and hulled)

Soybean oil, including epoxidized soybean oil (CAS No: 8001-22-7 and 8013-07-8)

Squalane (CAS No: 111-01-3): as a component of the adjuvant system

Starches normally found in food and food grade starches

Styrene-butadiene block copolymer (CAS No: 9003-55-8): with a butadiene limit of less than 1 ppm

Sulfolipo-cyclodextrin

Triethanolamine (CAS No: 102-71-6)

Tris(nonylphenyl)phosphite (CAS No: 26523-78-4)

Trometamol (CAS No: 77-86-1): for use in buffering systems at doses up to 0.65 mg/kg bw

Vanillin (CAS No: 121-33-5)

Vermiculite (CAS No: 1318-00-9), including expanded vermiculite

Zymosan A (CAS No: 58856-93-2): for use as an adjuvant at doses of up to 0.12 mg/kg bw

Normal foodstuffs

Avena (oats)

Carbohydrates naturally occurring

Cereals

Chocolate flavour

Coffea arabica

Honey

Lipids as constituents of the human diet

Royal jelly

Petroselinum crispum (parsley)

Peptides and proteins as constituents of the human diet

Pulses

⁴ Entry modified following the December 2020 CVMP plenary meeting

Chemically complex substances of natural origin

Organ autolysates

Immunoglobulines

Dried dialysate derived from blood

Lyophilised ruminal fluid

Natural substances essential for animal and human life

Oxygen (CAS No: 7782-44-7)

Substances that act by purely physical mechanisms

Cross-linked polyacrylamide hydrogel (CAS no. 9003-05-8), with impurity concentrations of acrylamide ≤ 1.5 ppm, and N,N,-methylene-bis-acrylamide ≤ 1 ppm, for intra-articular use in horses up to a dose of 0.08 ml/kg bw

Steel shot (CAS No: 7439-89-6): for use as weighting component in intraruminal devices