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Committee for Medicinal Products for Veterinary Use

Substances considered as not falling within the scope of Regulation (EC) No. 470/2009[1], with regard to residues of veterinary medicinal products in foodstuffs of animal origin

1. Background information

Regulation (EC) No. 470/2009 of 6 May 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 The Regulation repealed Council Regulation (EEC) No. 2377/90.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(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(3) of the Regulation states that:

> "This Regulation shall not apply 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 actives 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] Regulation (EC) No. 470/2009 of the European Parliament and of the Council of 6 May 2009, repealing Council Regulation (EEC) No. 2377/90

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

and manufacturing materials (EMEA/CVMP/072/97-Rev.1[2]), 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 posted to mrl@ema.europa.eu

[2] Initially adopted in April 1997 and further revised in July 2004

II. 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

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

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)

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

Diethylaminoethyl (DEAE)-Dextran (CAS No: 9013-34-7): at concentrations up to 150 mg/ml

Diethanolamine (CAS No: 111-42-2): at doses up to 0.3 mg/kg bw/day

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

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

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

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

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

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%

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)

Polybutene (CAS No: 9003-29-6)

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

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

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

Propolis

Propylene carbonate (CAS No: 108-32-7): at doses up to 1.4 mg/kg bw

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

Silicones (CAS No: 9006-65-9)

Simethicone (CAS No: 8050-81-5)

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

Sulfolipo-cyclodextrin

Triethanolamine (CAS No: 102-71-6)

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

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

Petroselium crispum (parsley)

Peptides and proteins as constituents of the human diet

Pulses

Chemically complex substances of natural origin

Organ autolysates

Immunoglobulines

Dried dialysate derived from blood

Lyophylised ruminal fluid

Natural substances essential for animal and human life

Oxygen (CAS No: 7782-44-7)

Biologically active constituents

Probiotic components including bacteria and yeasts

Stem cells