ANNEX I: LIST OF NAMES OF THE VETERINARY MEDICINAL PRODUCTS BASED ON BENZATHINE PENICILLIN FOR FOOD PRODUCING ANIMALS AND MARKETING AUTHORISATION HOLDERS IN EU MEMBER STATES, ICELAND AND NORWAY

Member State	Product trade name	Strength	Company name	Address
Austria	Duphapen	Benzathine benzylpenicillin 112.5 mg/ml Procaine benzylpenicillin 150.00 mg/ml	Wyeth-Lederle Pharma GmbH	Storchengasse 1 A-1150 Wien Austria
	Duplocillin	Benzathine benzylpenicillin 128.75 mg/ml Procaine benzylpenicillin 154.43 mg/ml	Intervet	Siemensstr. 105 A-1210 Wien Austria
	Serocillin Depot	Benzathine benzylpenicillin 112.5 mg/ml; Procaine benzylpenicillin 150.00 mg/ml	Norbrook Laboratories Limited	105 Armagh Rd Newry BT35 6PU, County Down Northern Ireland
	Norocillin Long acting	Benzathine benzylpenicillin 112.5 mg/ml; Procaine benzylpenicillin 150.00 mg/ml	Norbrook Laboratories Limited	105 Armagh Road Newry BT35 6PU, County Down Northern Ireland
Belgium	Peni-Kel L.A.	Benzathine benzylpenicillin 150,000 IU/ml Procaine benzylpenicillin 150,000 IU/ml	Kela Laboratória N.V.	St Lenaartseweg 48 B-2320 Hoogstraten Belgium
	Retardpen	Benzathine benzylpenicillin 150,000 IU/ml Procaine benzylpenicillin 150,000 IU/ml	V.M.D. N.V.	Berendonk 74 B-2370 Arendonk Belgium
	Emdopen 150+150 L.A.	Benzathine benzylpenicillin 150,000 IU/ml; Procaine benzylpenicillin 150,000 IU/ml; Procaine hydrochloride 20 mg/ml	Emdoka bvba	J. Lijsenstraat 16 B-2321 Hoogstraten Belgium
	Duplocilline L.A.	Benzathine benzylpenicillin 150,000 IU/ml Procaine benzylpenicillin 150,000 IU/ml	Intervet Belgium	Ragheno Park, Dellingstraat 32/1 B-2800 Mechelen Belgium
	Duphapen L.A.	Benzathine benzylpenicillin 150,000 IU/ml Procaine benzylpenicillin 150,000 IU/ml	Fort Dodge Animal Health Benelux BV	Van Houten Industriepark 25 NL-1381 MZ Weesp The Netherlands
Denmark	Duplocillin Vet	Benzathine benzylpenicillin 150,000 IU/ml Procaine benzylpenicillin 150,000 IU/ml	Intervet International bv	Wim de Körverstraat 35, P.O. Box 31 NL-5830 AA - Boxmeer The Netherlands
Finland	Duplocillin LA vet inj (150 mg/ml)	Benzathine benzylpenicillin 115 mg/ml; Procaine benzylpenicillin 150 mg/ml	Intervet Oy	Tuupakantie 7 A FIN-01740 Vantaa Finland

Member State	Product trade name	Strength	Company name	Address
France	Uniject	Benzathine benzylpenicillin 74 mg/ml Procaine benzylpenicillin 57 mg/ml Dihydrostreptomycin sulphate 64 mg/ml	Virbac S.A.	13ème rue – LID, BP 27 F-06511 Carros Cedex France
	Duphapen LA	Benzathine benzylpenicillin 15 mg/ml Procaine benzylpenicillin 15 mg/ml	Fort Dodge Santé Animal	22-24 Ave Marcel Dassault,B.P. 440 F-37204 Tours Cedex 3 France
	Duplocilline	Benzathine benzylpenicillin 150,000 IU/ml Procaine benzylpenicillin 150,000 IU/ml	Intervet	Rue Olivier de Serres, Angers Technopole F-49071 Beaucouzé France
	Dipene 5 + 5	Benzathine benzylpenicillin 100,000 IU/ml Procaine benzylpenicillin 100,000 IU/ml	Virbac S.A.	13ème rue – LID, BP 27 F-06511 Carros Cedex France
	Shotapen	Benzathine benzylpenicillin 100 mg/ml Procaine benzylpenicillin 100,000 IU/ml Dihydrostreptomycin sulphate 16.4 mg/ml	Virbac S.A.	13ème rue – LID, BP 27 F-06511 Carros Cedex France
Germany	Strepdipend Suspension ölig	Benzathine benzylpenicillin 91.67 mg/ml Procaine benzylpenicillin 30.0 mg/ml Dihydrostreptomycin sulphate 196.4 mg/ml	Serumwerk Bernburg AG	Hallesche Landstrasse 105b D-06406 Bernburg Germany
	Strepdipend Suspension wässrig	Benzathine benzylpenicillin 91.67 mg/ml Dihydrostreptomycin sulphate 157.15 mg/ml	Serumwerk Bernburg AG	Hallesche Landstrasse 105b D-06406 Bernburg Germany
	Veracin compositum	Benzathine benzylpenicillin 76.19 mg/ml Procaine benzylpenicillin 120.00 mg/ml Dihydrostreptomycin sulphate 258.0 mg/ml Procaine hydrochloride 20.0 mg/ml	Albert Albrecht GmbH & Co. KG	Hauptstrasse 6-8 D-88326 Aulendorf Germany
	Vetripen Depot N	Benzathine benzylpenicillin 76.19 mg/ml Procaine benzylpenicillin 118.69 mg/ml Dihydrostreptomycin sulphate 263.15 mg/ml	CEVA Tiergesundheit GmbH	Kanzlerstr. 4 D-40472 Düsseldorf Germany
	Langzeit-penicillin und Dihydrostreptomycin ad us. vet	Benzathine benzylpenicillin 76.19 mg/ml Procaine benzylpenicillin 120.00 mg/ml Dihydrostreptomycin sulphate 258.0 mg/ml	AniMedica GmbH	Im Südfeld 9 D-48308 Senden-Bösensell Germany
	Belamycin 300	Benzathine benzylpenicillin 127.0 mg/ml Procaine benzylpenicillin 149.9 mg/ml	Bela-Pharm	Lohner Str. 19 D-49377 Vechta Germany
Greece	Fatromiycine – S	Benzathine benzylpenicillin 150,000 IU/ml Procaine benzylpenicillin 150,000 IU/ml Dihydrostreptomycin sulphate 200 mg/ml	Fatro S.p.A.	Via Emilia 285 I-40064 Ozzano dell'Emilia - Bologna Italy

Member State	Product trade name	Strength	Company name	Address
Greece (cont.)	Hipracillin retard	Benzathine benzylpenicillin 100,000 IU/ml Procaine benzylpenicillin 100,000 IU/ml Dihydrostreptomycin sulphate 250 mg/ml	Laboratorios HIPRA S.A.	Av. La Selva 135 E-17170 Amer (Girona) Spain
Ireland	Norocillin LA	Benzathine benzylpenicillin 112.5 mg/ml; Procaine benzylpenicillin 150.00 mg/ml	Norbrook Laboratories Limited	105 Armagh Road Newry BT35 6PU, County Down Northern Ireland
	Duphapen LA	Benzathine benzylpenicillin 112.5 mg/ml; Procaine benzylpenicillin 150.00 mg/ml	Fort Dodge Animal Health Limited	Flanders Road, Hedge End Southampton SO30 4QH UK
Italy	Rubrocillina Forte Veterinaria	Benzathine benzylpenicillin 250,000 IU/ml Dihydrostreptomycin sulphate 100 mg/ml	Gellini International & Intervet Italy	Via Walter Tobagi, 7 I-20068 Peschiera Borromeo (MI) Italy
	Liquicil (3 different pack sizes all with same strength)	Liquicil 5 + 5: Benzathine benzylpenicillin 200,000 IU/ml Streptomycin sulphate 200 mg/ml Liquicil 20 + 20: Benzathine benzylpenicillin 200,000 IU/ml Streptomycin sulphate 200 mg/ml Liquicil 50 + 50: Benzathine benzylpenicillin 200,000 IU/ml Streptomycin sulphate 200 mg/ml	A.C.R.A.F. S.p.A. - Aziende Chimiche Riunite Angelini Francesco	P.le della Stazione snc I-00040 S. Palomba-Pomezia - Roma Italy
	Ritardomicina	Benzathine benzylpenicillin 6,000,000 IU/ml Dihydrostreptomycin sulphate 20 mg/ml Streptomycin sulphate 20 mg/ml	Azienda Farmaceutica Italiana S.r.l.	Via A. De Gasperi 47 I-21040 Sumirago (VA) Italy

Member State	Product trade name	Strength	Company name	Address
Italy (cont.)	Fatromicina Ritardo (3 strengths)	Srength: 1 + 1: Benzathine benzylpenicillin 5000 IU/ml Sodium benzylpenicillin 30,000 IU/ml Procaine benzylpenicillin 20,000 IU/ml Dihydrostreptomycin sulphate 133.5 mg/ml Strength 3 + 2.5: Benzathine benzylpenicillin 150,000 IU/ml Sodium benzylpenicillin 75,000 IU/ml Procaine benzylpenicillin 75,000 IU/ml Dihydrostreptomycin sulphate 333.7 mg/ml Strength 6 + 5: Benzathine benzylpenicillin 150,000 IU/ml Sodium benzylpenicillin 90,000 IU/ml Procaine benzylpenicillin 60,000 IU/ml Dihydrostreptomycin sulphate 333.75 mg/ml	Fatro S.p.A.	Via Emilia 285 I-40064 Ozzano dell'Emilia - Bologna Italy
	Lugabiotic (4 pack sizes – all with same strength)	Flacone 1 + 1: Benzathine benzylpenicillin 166,667 IU/ml Sodium benzylpenicillin 66,667 IU/ml Procaine benzylpenicillin 100,000 IU/ml Streptomycin sulphate 333 mg/ml Flacone 3 + 3: Benzathine benzylpenicillin 166,667 IU/ml Sodium benzylpenicillin 66,667 IU/ml Procaine benzylpenicillin 100,000 IU/ml Streptomycin sulphate 333 mg/ml Flacone 6 + 6: Benzathine benzylpenicillin 166,667 IU/ml Sodium benzylpenicillin 66,667 IU/ml Procaine benzylpenicillin 100,000 IU/ml Streptomycin sulphate 333 mg/ml Flacone 10 + 10: Benzathine benzylpenicillin 166,667 IU/ml Sodium benzylpenicillin 66,667 IU/ml Procaine benzylpenicillin 100,000 IU/ml Streptomycin sulphate 333 mg/ml	Fatro S.p.A.	Via Emilia 285 I-40064 Ozzano dell'Emilia - Bologna Italy
	Neotardocillina 12,5%	Benzathine benzylpenicillin 125,000 IU/ml Streptomycin sulphate 50 mg/ml	VAAS Industria Chimica Farmaceutica Srl	Via Siena, 268 I-47032 Capocolle di Bertinoro (FC) Italy

Member State	Product trade name	Strength	Company name	Address
Italy (cont.)	Gentaplus	Benzathine benzylpenicillin 200,000 IU/ml Gentamicin sulphate 30 mg/ml	IZO	Via Cremona 282 I-25124 Brescia Italy
	Bicormicina L.A.	Benzathine benzylpenicillin 125,000 IU/ml Procaine benzylpenicillin 125,000 IU/ml Dihydrostreptomicin sulphate 250 mg/ml Dexamethasone sodium phosphate 200 µg/ml Dexamethasone 21-isonicotinate 200 µg/ml	Fatro S.p.A.	Via Emilia 285 I-40064 Ozzano dell'Emilia - Bologna Italy
	Liquibiotic iniettabile (3 pack sizes with same strength)	Tipo 5 + 5 Benzathine benzylpenicillin 200,000 IU/ml Streptomycin sulphate 200 mg/ml Tipo 20 + 20 Benzathine benzylpenicillin 200,000 IU/ml Streptomycin sulphate 200 mg/ml Tipo 50 + 50 Benzathine benzylpenicillin 200,000 IU/ml Streptomycin sulphate 200 mg/ml	Industria Italiana Integratori TREI spA	Via Pietro. Bembo, 12 I-41100 Modena Italy
Luxembourg	Duplocilline LA inj.	Benzathine benzylpenicillin 150,000 IU/ml Procaine benzylpenicillin 150,000 IU/ml	Intervet International B.V. (NL)	Ragheno Park, Dellingstraat 32/1 B-2800 Mechelen Belgium
	Duphapen LA inj.	Benzathine benzylpenicillin 600,000 IU/ml	Fort Dodge Animal Health Benelux BV	Van Houten Industriepark 25 NL-1381 MZ Weesp The Netherlands
Netherlands				
Portugal	Bicormicina L.A.	Benzathine benzylpenicillin 125,000 IU/ml Procaine benzylpenicillin 125,000 IU/ml Dihydrostreptomicin sulphate 250 mg/ml Dexamethasone sodium phosphate 200 µg/ml Dexamethasone 21-isonicotinate 200 µg/ml	Univete – Técnica Pécuária Comércio e Indústria, Lda	Rua D. Jerónimo Osório, 5-B P-1400-119 Lisboa Portugal
	Duplocilina L.A.	150,000 IU/ml	Intervet Portugal Saúde Animal	Estrada Nacional 249, Km 14,2 Mem Martins Portugal
	Peni-Kel L.A.	150,000 IU/ml	Kela Laboratória NV	St. Lenaartseweg 48 B-2320 Hoogstraten Belgium

Member State	Product trade name	Strength	Company name	Address
Portugal (cont.)	Shotapen L.A.	100,000 IU/ml	Virbac España S.A.	Angel Guimerá 179 a 181 E-08950 Esplugues de Llobregat, Barcelona Spain
Spain	Ivensalpen retardado	Benzathine benzylpenicillin 200,000 IU/ml; Procaine benzylpenicillin 40,000 IU/ml; Benzylpenicillin 60,000 IU/ml	Laboratorios e Industrias IVEN, S.A.	Luis I, 56-58 Polígono Industrial De Vallecas E-28031 Madrid Spain
	Ivensalpen E (Ivensalpen sulfamidico)	Benzathine benzylpenicillin 50,000 IU/ml Procaine benzylpenicillin 50,000 IU/ml Sulphamethoxypiridazine 200 mg/ml	Laboratorios e Industrias IVEN, S.A.	Luis I, 56-58 Polígono Industrial De Vallecas E-28031 Madrid Spain
	Zoobencil Estrepto 1 (Product currently suspended)	(Same composition as Zoobencil Estrepto 2, different volume.)	Vétoquinol Especialidades Veterinarias, S.A.	Edificio Italia Parque Empresarial San Fernando E-28830 San Fernando de Henares, Madrid Spain
	Zoobencil Estrepto 2	Benzathine benzylpenicillin 2,000,000 IU/ml; Streptomycin (sulphate) 200 mg/ml;	Vétoquinol Especialidades Veterinarias, S.A.	Edificio Italia Parque Empresarial San Fernando E-28830 San Fernando de Henares, Madrid Spain
	Zoobencil B12	Benzathine benzylpenicillin 3,000,000 IU/ml Vitamin B12: 37.5 µg/ml	Vétoquinol Especialidades Veterinarias, S.A.	Edificio Italia Parque Empresarial San Fernando E-28830 San Fernando de Henares, Madrid Spain
	Dipen Suspensión retard	Benzathine benzylpenicillin 100,000 IU/ml Procaine benzylpenicillin 100,000 IU/ml Dihydrostreptomycin 250 mg/ml	Chemical Iberica	Crta Burgos-Portugal, km. 256 E-37448 Calzada de Don Diego, Salamanca Spain
	Hiprabenzatina -1	Benzathine benzylpenicillin 1,000,000 IU/ml Dihydroxystreptomycin 1000 mg/ml	Laboratorios HIPRA S.A.	Avda. La Selva, 135 E-17170 Amer (Girona) Spain
	Hipracilina retard	Benzathine benzylpenicillin 100,000 IU/ml; Procaine benzylpenicillin 100,000 IU/ml; Dihydrostreptomycin (sulphate) 50 mg/ml	Laboratorios HIPRA S.A.	Avda. La Selva, 135 E-17170 Amer (Girona) Spain
	Dipenisol retard	Benzathine benzylpenicillin 100,000 IU/ml Procaine benzylpenicillin 100,000 IU/ml Dihydrostreptomycin (sulphate) 200 mg/ml	Química Farmacéutica Bayer, S.A.	Calabria, 268 E-08029 Barcelona Spain
	Shotapen LA 250	Benzathine benzylpenicillin 100,000 IU/ml Procaine benzylpenicillin 100,000 IU/ml Dihydrostreptomycin (sulphate) 200 mg/ml	Virbac España SA	Angel Guimerá, 179-181 E-08950 Esplugues de Llobregat, Barcelona Spain

Member State	Product trade name	Strength	Company name	Address
Spain (cont.)	Benzatard	Benzathine benzylpenicillin 150,000 IU/ml; Procaine benzylpenicillin 150,000 IU/ml	Laboratorios SYVA, S.A.	Avda. Párroco Pablo Díez, 49-57 E-24010 León Spain
	Biosuspen retard	Benzathine benzylpenicillin 75,000 IU/ml; Procaine benzylpenicillin 125,000 IU/ml Dihydrostreptomycin (sulphate) 250 mg/ml Dexamethasone(21-Naphosphate) 250 µg/ml	Laboratorios SYVA, S.A.	Avda. Párroco Pablo Díez, 49-57 E-24010 León Spain
	Biochoc	Benzathine benzylpenicillin 1,000,000 IU/ml; Procaine benzylpenicillin 1,000,000 IU/ml; Sodium benzylpenicillin 500,000 IU/ml; Dihydrostreptomycin (sulphate) 5000 mg/ml	Laboratorios SYVA, S.A.	Avda. Párroco Pablo Díez, 49-57 E-24010 León Spain
	Benzatina E	Benzathine benzylpenicillin 75,000 IU/ml; Potassium benzylpenicillin 25,000 IU/ml Procaine benzylpenicillin 50,000 IU/ml Streptomycin (sulphate) 250 mg/ml	Laboratorios Ovejero, S.A.	L-1 Crtra. León-Vilecha, 30 Apartado 321 E-24080 León Spain
	Cyapen retard	Benzathine benzylpenicillin 100,000 IU/ml; Procaine benzylpenicillin 100,000 IU/ml Dihydrostreptomycin (sulphate) 200 mg/ml	Virbac España S.A.	Angel Guimerá, 179-181 E-08950 Esplugues de Llobregat, Barcelona Spain
Sweden				
United Kingdom	Duphapen LA	Benzathine benzylpenicillin 112.5 mg/ml; Procaine benzylpenicillin 150.00 mg/ml	Fort Dodge Animal Health Limited	Flanders Road, Hedge End Southampton SO30 4QH UK
	Norocillin LA	Benzathine benzylpenicillin 112.5 mg/ml; Procaine benzylpenicillin 150.00 mg/ml	Norbrook Laboratories Ltd	105 Armagh Road Newry BT35 6PU, County Down Northern Ireland
Iceland	Duplocillin L.A. vet	Benzathine benzylpenicillin 115 mg/ml; Procaine benzylpenicillin 150 mg/ml	Intervet International B.V.	Lynghals 13 IS-110-Reykjavik Iceland
Norway				

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR SUSPENSION OF THE MARKETING AUTHORISATIONS

1. Introduction

Benzylpenicillin is a bactericidal antibiotic with a spectrum of activity against most Gram-positive bacteria, Gram-negative cocci and some other Gram-negative bacteria, spirochaetes and actinomycetes. It is not active against penicillinase-producing strains. Minimum inhibitory concentrations of benzylpenicillin are generally low. The *in vitro* MICs for sensitive organisms are in the range of 0.06 µg/ml and 0.125 µg/ml. Gram-positive bacteria are more susceptible than Gram-negatives. The bactericidal action of benzylpenicillin is time-dependent (concentration-independent). Therefore, serum levels above the breakpoint must be maintained for a significant proportion of the dosing interval.

On 3 October 2001 the Irish Medicines Board presented to the EMEA a referral under Article 20 of Council Directive 81/851/EEC as amended, concerning the Marketing Authorisations for all veterinary medicinal products containing benzathine benzylpenicillin injectable formulations intended for administration to food producing species. Following a decision of the Irish Medicines Board to suspend Marketing Authorisations of benzathine benzylpenicillin containing slow release injectable preparations in Ireland since residues of (benzyl)penicillin above the maximum residue limit were shown to remain in tissues (injection sites) of treated animals beyond the expiry of the withdrawal period, the CVMP was requested to give its opinion as to whether, given the residue depletion data and published literature available concerning the depletion of residues of benzathine benzylpenicillin when administered by injection, the withdrawal period should be extended from the standpoint of Community Interest in safeguarding consumer safety.

2. Establishment of MRLs for Penicillin

Several cases of allergic reactions in humans following the ingestion of food containing penicillin residues were reviewed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Reports of further cases which were not available to JECFA had also been reported in the published literature. It was evident that penicillin residues have caused allergic reactions in consumers and that some of these reactions have been serious.

In setting MRLs for the penicillins, the CVMP adopted the same approach as JECFA. Being aware of cases of allergic reactions at very low doses, JECFA recommended that the daily intake of benzylpenicillin from food be kept as low as practicable, and in any case below 30 µg. The CVMP set MRLs such that consumer intake from all foods would not exceed this 30 µg threshold. Thus, the MRLs established by the CVMP were 50 µg/kg for edible tissues. The recommendation was based on the results of studies in humans, whilst JECFA was aware that this ADI does not absolutely remove the risk to exquisitely sensitive individuals. Thus, the ADI for benzylpenicillin was not based on a no-observed-effect-level in a long-term study in the most sensitive species, which is the most commonly used procedure for setting ADIs, and which would reflect a life-time exposure to the substance. Instead, the ADI was based on an approach considering the acute allergic effects of benzylpenicillin in humans, since these were considered to be the most relevant factor in the safety evaluation of benzylpenicillin.

3. Residues depletion studies

The residues depletion studies in cattle which were carried out before 1990 used bioassays which were not validated. Residues were extracted from tissues using aqueous rather than solvent-based systems. The procedures did not include a deproteination step or a step to hydrolyse benzathine benzylpenicillin to benzylpenicillin. Consequently the residues were probably underestimated. Notwithstanding these deficiencies, residues of up to 246 µg/kg were found in the injection site 45 days after dosing in one study and residues of up to 678 µg/kg were found at the injection site 56 days after the last dose of a commercial preparation in another study. Following the identification of the problems associated with

the bioassays, new studies were carried out using more appropriate analytical techniques. In one study, residues of up to 2270 µg/kg (more than 45 times the MRL of 50 µg/kg) were found in injection site tissue at the last time point, 42 days after treatment. In another study residues of up to 643 µg/kg (more than 12 times the MRL) were found in injection site tissue at the last time point, 50 days after treatment. The residue concentrations at the injection site were very variable indicating considerable inter-animal variation; as a consequence, in some studies, no time-dependent decrease in residue concentrations was apparent. None of the available studies can be used as a basis for establishing withdrawal periods in cattle.

The residues depletion studies which were carried out in pigs before 1990 used bioassays which were not validated. Residues were extracted from tissues using aqueous rather than solvent-based systems and the procedures did not include a deproteination step or a step to hydrolyse benzathine benzylpenicillin to benzylpenicillin. Consequently the residues were probably underestimated. Notwithstanding these deficiencies, in one study, residues exceeding the MRL of 50 µg/kg were present in injection site tissue up to and including the last time point investigated (72 days). More recent studies were carried out using appropriate analytical methodology. In one study, residues of up to 122 µg/kg (more than twice the MRL of 50 µg/kg) were found in injection site tissue at the last time point, 35 days after treatment. In another study residues of up to 279 µg/kg (more than 5 times the MRL) were found in injection site tissue at the last time point, 50 days after treatment. Moreover the magnitude of the residues at the injection side was extremely variable demonstrating considerable inter-animal variation. For some studies, there was no clear tendency for the residue concentrations to decrease in a time-dependent manner. None of the studies can be used as a basis for establishing withdrawal periods in pigs.

The residues depletion studies carried out in sheep prior to 1990 suffer from the same deficiencies as the early studies in cattle and pigs, namely the lack of a satisfactory extraction procedure, the absence of deproteinisation step and the use of non-validated bioassays. With these deficiencies residues in injection site tissue were shown to be extremely variable and persistent. In one study residues in injection site tissue taken 42 days after treatment ranged from less than 3 µg/kg to up to 40,260 µg/kg (over 800 times the MRL value). In a more recent study, residues in the range from 20.7 up to 649 µg/kg (over 12 times the MRL value) were reported 35 days after treatment (the last time point). None of the studies can be used as a basis for establishing withdrawal periods in sheep.

No residues depletion data were available to the CVMP for the other species for which Marketing Authorisations exist, such as horses, goats and poultry.

None of the available residue depletion studies substantiated the withdrawal times currently applied to injectable benzathine benzylpenicillin-containing products in Member States.

4. Conclusions and recommendations

Valid scientific data substantiating withdrawal periods for long-acting benzathine benzylpenicillin injectable veterinary drugs are not available for the products authorised in the European Union.

Data made available by CVMP members, by National Authorities of Member States, literature data, as well as data from residue depletion studies conducted by marketing authorisation holders, indicate that currently authorised withdrawal periods do not ensure that residues in injection sites decrease to below the maximum residue limit of 50 µg/kg for benzylpenicillin.

In the absence of adequate data for the establishment of appropriate withdrawal periods, it is prudent to assume that consumers can be exposed to benzylpenicillin residues in excess of the MRL, following the use of benzathine benzylpenicillin in depot formulations. Such residues present a hazard to the consumer, particularly those who are sensitised to penicillin.

Having considered the residue depletion data and published literature available concerning the depletion of residues of benzylpenicillin when administered by injection as the benzathine form, the CVMP concluded that it was not possible on the basis of the data available to establish withdrawal periods.

Where there exists no authorized medicinal products for a condition, Member States may exceptionally, in particular in order to avoid unnecessary suffering to the animals concerned, permit the administration by a veterinarian or under his/her direct personal responsibility to an animal or to a small number of animals, a veterinary medicinal product authorized in the Member State concerned for use in another animal species. In such circumstances, the meat withdrawal period should be not less than 28 days. The CVMP considered that the stipulated withdrawal period of 28 days would not be adequate to ensure that residues at the injection site would have depleted to below the MRL. Therefore, if continued use of these products is to be permitted for companion animals there must be an absolute contra-indication for use in food-producing species.

For the purposes of this referral, the CVMP was requested to give its opinion with regard to the withdrawal period. Consequently a comprehensive assessment of the available data concerning the efficacy of benzathine benzylpenicillin was not made. However the CVMP noted that plasma concentrations of benzylpenicillin were sub-therapeutic compared to the *in vitro* MIC values for many organisms. The occurrence of sub-therapeutic plasma concentrations of antibiotics is regarded as an important factor in the development of resistance. The CVMP therefore considered that, should adequate residues depletion data become available which would permit the establishment of a withdrawal period, then the efficacy of the products concerned would need to be confirmed at the doses administered in such residues depletion studies.

5. Overall Recommendations

Having considered the residue depletion data and published literature available concerning the depletion of residues of benzylpenicillin when administered by injection as the benzathine form, the CVMP concluded that:

- it was not possible to establish a withdrawal period based on the available data;
- the currently authorised withdrawal periods are inadequate to ensure that residues at the injection site do not exceed the MRL;
- the currently authorised withdrawal periods are inadequate to ensure that foodstuffs obtained from the treated animal do not contain residues which might constitute a health hazard to the consumer;
- Marketing Authorisations for all injectable veterinary medicinal products based on benzathine benzylpenicillin and intended for administration to food producing species should be suspended;
- the SPCs and product literature for all injectable veterinary medicinal products based on benzathine benzylpenicillin, which are indicated for administration to companion animals, should contain an absolute contra-indication for their use in food-producing species.
- The CVMP should review the grounds for suspension after one year, or as soon as new data are submitted to the Committee for evaluation.