Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal products, animal species, route of administration, applicants and marketing authorisation holders in the Member States

Member State EU / EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000 mg/g Arzneimittel-Vormischung zur Herstellung von Fütterungsarzneimitteln für Ferkel	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Belgium	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000 mg/g premix voor gemedicineerd voeder	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Bulgaria	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000 mg/g premix for medicated feeding stuff for piglets	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Bulgaria	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	ZINCOPREMIX 1000 mg/g	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Cyprus	Laboratorios Calier, S.A. C/ Barcelonès, 26 Pla del Ramassà Les Franqueses del Vallès 08520 Barcelona Spain	OXIDO DE ZINC CALIER 1000 mg/g, πρόμιγμα για φαρμακούχο ζωοτροφή για χοίρους	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Cyprus	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	ZINCOPREMIX 1000MG/G πρόμιγμα για φαρμακούχο ζωοτροφή για χοίρους	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Cyprus	Vetpharma Animal Health, S.L. C/ Les Corts, 23. 08028 Barcelona Spain	ZINTESTIN 1000MG/G πρόμιγμα για φαρμακούχο ζωοτροφή για χοίρους	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

Czech Republic	Trouw Nutrition Biofaktory s.r.o. Na Chvalce 2049 193 00 Praha 9 Horní Počernice Czech Republic	BIOZINK 600 mg/g premix pro medikaci krmiva pro selata	Zinc oxide	600 mg/g	Premix	Pigs (piglets)	Oral
Czech Republic	Tekro, spol. s r.o. Višňová 2/484 140 00 Praha 4 Czech Republic	MEDITEK Zn 500 mg/g perorální prášek	Zinc oxide	622 mg/g	Oral powder	Pigs (piglets)	Oral
Czech Republic	Tekro, spol. s r.o. Višňová 2/484 140 00 Praha 4 Czech Republic	MEDITEK Zn 500 mg/g premix pro medikaci krmiva	Zinc oxide	622 mg/g	Premix	Pigs (piglets)	Oral
Czech Republic	MIKROP ČEBÍN a.s. Čebín 416 664 23 Čebín Czech Republic	MIKROP – VLP ZINEK premix	Zinc oxide	492 mg/g	Premix	Pigs (piglets)	Oral
Czech Republic	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	ZINCOPREMIX 1000 mg/g premix pro medikaci krmiva pro prasata	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Denmark	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Denmark	Vepidan ApS Østerbrogade 23 DK-9670 Løgstør Denmark	VetZink	Zinc oxide	1000 mg/g	Oral powder	Pigs (piglets)	Oral
Denmark	Vepidan ApS Østerbrogade 23 DK-9670 Løgstør Denmark	VetZink	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Denmark	Vilofarm A/S Sjellebrovej 10 DK-8544 Mørke Denmark	Vilocare	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

Denmark	Vilofarm A/S Søagervej 9, Sdr. Onsild DK-9500 Hobro Denmark	Zicare	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Denmark	Vilofarm A/S Søagervej 9, Sdr. Onsild DK-9500 Hobro Denmark	Zicare	Zinc oxide	1000 mg/g	Oral powder	Pigs (piglets)	Oral
Denmark	ScanVet Animal Health A/S Kongevejen 66 DK-3480 Fredensborg Denmark	Zingovet	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Denmark	ScanVet Animal Health A/S Kongevejen 66 DK-3480 Fredensborg Denmark	Zingovet	Zinc oxide	1000 mg/g	Oral powder	Pigs (piglets)	Oral
Denmark	Vepidan ApS Østerbrogade 23 DK-9670 Løgstør Denmark	Zinkoxid Vepidan	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Estonia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Finland	Vepidan ApS Østerbrogade 23 DK-9670 Løgstør Denmark	Vetzin vet. 1000 mg/g esisekoite lääkerehua varten	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
France	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	GUTAL PREMELANGE MEDICAMENTEUX POUR PORCELETS	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Germany	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Germany	aniMedica GmbH Im Südfeld 9 D-48308 Senden-Bösensell Germany	Enteroxid N AMV aniMedica	Zinc oxide Colistin sulfate	480 mg/g 25 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

Germany	aniMedica GmbH Im Südfeld 9 D-48308 Senden-Bösensell Germany	aniMedica Enteroxid N	Zinc oxide Colistin sulfate	480 mg/g 25 mg/g	Powder for oral administration	Pigs (piglets)	Oral
Hungary	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000 mg/g gyógypremix malacok számára A.U.V.	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Hungary	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	ZINCOPREMIX 1000 mg/g gyógypremix sertések számára A.U.V.	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Hungary	Sintofarm S.p.A. Via Togliatti 5 42016 Guastalla (RE) Italy	ZINCOSINT G 1000 mg/g gyógypremix sertések részére A.U.V.	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Hungary	Dunavet-B Zrt. Dolgos u. 2 1126 Budapest Hungary	Zintestin Forte 1000 mg/g gyógypremix sertések részére A.U.V.	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Iceland	Vepidan ApS Østerbrogade 23 DK-9670 Løgstør Denmark	VetZin	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Ireland	DSM Nutritional Products (UK) Limited Delves Road Heanor Gate Industrial Estate Heanor Derbyshire, DE75 7SG United Kingdom	Pigzin Premix, 100% w/w Premix for medicated feeding stuff.	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Ireland	Provimi Limited Eastern Avenue Lichfield Staffordshire WS13 7SE United Kingdom	ZincoTec – Zinc Oxide 100% Premix for medicated Feeding Stuff.	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

Ireland	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000 mg/g premix for medicated feeding stuff for piglets	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Italy	Laboratorios Calier, S.A. C/ Barcelonès, 26 Pla del Ramassà Les Franqueses del Vallès 08520 Barcelona Spain	OXIDO DE ZINC	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Italy	Vetpharma Animal Health, S.L. C/ Les Corts, 23. 08028 Barcelona Spain	ZINTESTIN	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Italy	Sintofarm S.p.A. Via Togliatti 5 42016 Guastalla (RE) Italy	ZINCOFARM G	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Italy	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	ZINCOPREMIX	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Italy	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	GUTAL 1000 mg/g	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Latvia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Lithuania	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	GUTAL 1 000 mg/g, vaistinis premiksas paršeliams	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
The Netherlands	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	GUTAL 1000 mg/ g premix for piglets	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

Norway	Vepidan ApS Østerbrogade 23 DK-9670 Løgstør Denmark	VetZin	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Poland	Vetoquinol Biowet Sp. z o. o. ul. Kosynierów Gdyńskich 13-14 66-400 Gorzów Wielkopolski Poland	Suibicol Premiks (30 g + 18,45 g)/100 g premiks do sporządzania paszy leczniczej dla świń	Zinc oxide Sulfaguanidinum	30 g/100 g 18,45 g/100 g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Poland	Laboratorios Calier, S.A. C/ Barcelonès, 26 Pla del Ramassà Les Franqueses del Vallès 08520 Barcelona Spain	Tlenek cynku Calier 1000 mg/1g, premiks do sporządzania paszy leczniczej dla świń	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Poland	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	Zincopremix 1000 mg/g premiks do sporządzania paszy leczniczej dla świń	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Poland	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000g/ kg premix for medicated feeding staff	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Poland	Vetoquinol Biowet Sp. z o. o. ul. Kosynierów Gdyńskich 13-14 66-400 Gorzów Wielkopolski Poland	Suibicol proszek	Zinc oxide Sulfaguanidine	30 g/100 g 18,45 g/100 g	Oral powder	Pigs (piglets)	Oral
Portugal	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000 mg/g premix for medicated feeding stuff for piglets	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Portugal	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	APSAMIX ZINC 1000 mg/g medicated premix for pigs	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

Portugal	CALIER PORTUGAL, S.A. Centro Empresarial Sintra-Estoril II, Ed. C, R. Pé de Mouro Estrada de Albarraque 2710 - 335 Sintra Portugal	OXIDO DE ZINCO CALIER 1000 mg/g Pré-mistura medicamentosa para suínos (leitões)	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Portugal	Vetlima S.A. Centro Empresarial da Rainha, Lote 27 2050-501 Vila Nova da Rainha Portugal	Vetazinco 1000 mg/g Pré-mistura medicamentosa para suínos (leitões)	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Romania	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	Zincopremix 1000 mg/g premix pentru furaje medicamentate la porcine	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Romania	Sintofarm S.p.A. Via Togliatti 5 42016 Guastalla (RE) Italy	Zincosint G 1000 mg/g premix pentru furaje medicamentate la porcine	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Romania	S.C. CRIDA PHARM S.R.L. 2 Intrarea Vagonetului, Bl. 101, Ap. 47 sector 6, Bucharest Romania	Colistop premix 1000 mg/g premix medicamentat pentru purcei dupa intarcare	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Slovak Republic	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	Zincopremix 1000 mg/g premix na medikovanie kŕmnej zmesi pre ošípané	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Slovak Republic	Tekro, spol. s r.o. Višňová 2/484 140 00 Praha 4 Czech Republic	Tekrozink 500 mg/g perorálny prášok	Zinc oxide	622 mg/g (500 mg zinc/g)	Pulvis for oral use	Pigs (piglets)	Oral
Slovak Republic	Tekro, spol. s r.o. Višňová 2/484 140 00 Praha 4 Czech Republic	Tekrozink 500 mg/g premix na medikáciu krmiva	Zinc oxide	622mg/g (500 mg zinc/g)	Premix for medicated feedingstuff	Pigs (piglets)	Oral

Slovak Republic	Trouw Nutrition Biofaktory s.r.o. Na Chvalce 2049 193 00 Praha 9 Horní Počernice Czech Republic	Biozink 600 mg/g premix na medikáciu krmiva	Zinc oxide	600 mg/g	Premix for medicated feedingstuff	Pigs (piglets)	Oral
Slovenia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000 mg/g predmešanica za pripravo zdravilne krmne mešanice za pujske	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Spain	Industrial Veterinaria, S.A. Esmeralda, 19 E-08950 Esplugues de Llobregat (Barcelona) Spain	ZETAPREX	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Spain	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	ZINCOPREMIX 1000 MG/G	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Spain	Laboratorios Support Pharma, S.L. General Alvarez de Castro, 39 28010 Madrid Spain	ZINCOSINT G 100 MG/G PREMIX	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Spain	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1.000 mg/g premezcla medicamentosa para lechones	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Spain	Laboratorios Calier, S.A. C/ Barcelonès, 26 Pla del Ramassà Les Franqueses del Vallès 08520 Barcelona Spain	ÓXIDO DE ZINC CALIER 1000 mg/g PREMEZCLA MEDICAMENTOSA PARA CERDOS	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

Spain	Vetpharma Animal Health, S.L. C/ Les Corts, 23. 08028 Barcelona Spain	ZINTESTIN 1000 mg/g Premezcla medicamentosa para porcino	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Spain	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	APSAMIX ZINC 1000 mg/g premezcla medicamentosa para porcino	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Spain	Andrés Pintaluba, S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana 5 43206 Reus (Tarragona) Spain	ZINCOTRAX	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Sweden	Vepidan ApS Østerbrogade 23 DK-9670 Løgstør Denmark	Vetzin vet	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
Sweden	Biovet ApS Kongevejen 66 3480 Fredensborg Denmark	Zingovet	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
United Kingdom	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Gutal 1000 mg/g premix for medicated feeding stuff for piglets	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral
United Kingdom	DSM Nutritional Products (UK) Limited Delves Road Heanor Gate Industrial Estate Heanor Derbyshire, DE75 7SG United Kingdom	Pigzin Premix, 100% w/w Premix for Medicated Feeding Stuff	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

United Kingdom	SCA NuTec (Provimi Ltd) Eastern Avenue Lichfield Staffordshire WS13 7SE United Kingdom	ZincoTec Zinc Oxide 100% Premix for Medicated Feeding Stuff	Zinc oxide	1000 mg/g	Premix for medicated feeding stuff	Pigs (piglets)	Oral

Annex II

Scientific conclusions and grounds for the refusal of the marketing authorisation and for withdrawal of the existing marketing authorisations

Overall summary of the scientific evaluation of veterinary medicinal products containing zinc oxide to be administered orally to food producing species (see Annex I)

1. Introduction

During the weaning period, piglets loose the benefit of passive immunity from the sow's milk and experience gastrointestinal changes that accompany the change in diet, which causes them a degree of stress and leaves them vulnerable to secondary infections. The degree of stress experienced during the weaning period in piglets varies with age of weaning (more stress in younger piglets) and husbandry conditions, and can influence the severity of post-weaning diarrhoea.

Veterinary medicinal products containing zinc oxide are used for the treatment and/or prevention and control of post-weaning diarrhoea in piglets. Different indications and dosages are currently recommended, but zinc oxide is mainly used in the feed at a dosage of 100 mg per kg body weight (bw) per day for 14 consecutive days, that is 2500 ppm zinc in feed.

In 2015 following a referral procedure (EMEA/V/A/108) under Article 33(4) of Directive 2001/82/EC, for Gutal 1000 g/kg premix for medicated feeding stuff for piglets (thereafter called 'Gutal')[1], a risk to the environment has been identified due to accumulation of zinc, in the terrestrial and aquatic compartment (including sediment), with acidic, sandy, well-drained soils being most vulnerable. In the frame of the aforementioned procedure, the Committee for Medicinal Products for Veterinary Use (CVMP) considered that there is some uncertainty associated with the calculated risks for some environmental compartments as the predicted environmental concentration (PEC) due to the use of zinc as a veterinary medicinal product could not be validated, and the predicted no effect concentration (PNEC) did not always account for zinc bioavailability (specifically for the sediment compartment). Although there were uncertainties in both PEC and PNEC calculations on environmental compartments, the overall risk assessment was viewed as conservative and as a result various risk mitigation measures were proposed, which were anticipated to reduce the accumulation of zinc in the environment.

On 1 February 2016, the Netherlands and France presented to the European Medicines Agency a referral notification in accordance with Article 35 of Directive 2001/82/EC for veterinary medicinal products containing zinc oxide to be administered orally to food producing species, due to concerns related to the risk to the environment and the potential increase of prevalence of antibiotic resistant bacteria from the use of products containing zinc oxide. The CVMP was requested to review all available data and to evaluate the overall benefit-risk balance of the products concerned in order to determine the benefits associated with the use of zinc oxide in food producing species and also the risks for the environment and risks of (co-)selection of resistance genes.

2. Discussion of data available

Assessment of potential benefits associated with the use of zinc oxide in food producing animals

Zinc oxide as a sole active substance

Several marketing authorisation holders provided proprietary studies for veterinary medicinal products containing zinc oxide as single active substance. Scarce information with only summaries of study

[1] CVMP opinion on Article 33(4) referral for Gutal 1000 g/kg premix for medicated feeding stuff for piglets (Procedure no. EMEA/V/A/108) - link

results was submitted and study methods were poorly reported (no study protocols, no raw data, no statistical analysis).

A summary of results from a study performed by Johansen *et al.* in Denmark in 2007[2] considering the effects of zinc oxide on post weaning diarrhoea in piglets have been provided. The study was a non-Good Clinical Practice (GCP) single-farm comparative study conducted with 3200 piglets. In the absence of relevant diagnostic data it was not possible to identify the pathogens involved. The study showed that feed to which 2.5% acid was added in combination with 2500 ppm zinc during the first 14 days post-weaning significantly reduced the prevalence of diarrhoea and the mortality of piglets.

The published data from Hu *et al.* (Hu *et al.,* 2013a[3]; Hu *et al.*, 2013b[4]) showed in two different non-GCP studies a statistically significant effect on faecal consistency (scored from 1 to 5) of the feed supplementation with 2250 ppm zinc in weaned piglets (aged 21 days) for 14 days, in comparison with a negative control.

In the study from Trckova *et al.* (2015)[5], clinical observation of weaned piglets challenged with enterotoxic *E. coli* demonstrated a lower diarrhoea score and diarrhoea incidence in the treated animals (fed with a diet containing 2500 ppm zinc oxide in feed) than in the control animals (untreated pigs). The zinc oxide supplementation was given for three weeks from weaning and the challenge performed four days after weaning.

Considering the duration of the administration of high amounts of zinc in the feed of weaned piglets (between 2500 and 3000 ppm of zinc), Hollis (2000)[6] advises that administration of high zinc content feed should not be prolonged for more than two weeks after weaning, and that zinc used should be in the form of zinc oxide. Higher yields were described in animals treated with 3000 ppm zinc in the first 21 days after weaning than in control animals, but the animals treated with zinc showed signs of toxicity in the three following weeks. Also, according to Mateos *et al.*, 1998[7] zinc supplement should not be prolonged further than the weaning period.

In a study on the administration of zinc oxide in weaned piglets (Poulsen, 1995)[8], the administration of high amounts of zinc as zinc oxide for a duration of 1, 2 or 3 weeks after weaning affected the incidence of post-weaning diarrhoea, among other parameters. The study was performed on 260 piglets from 36 litters weaned at the age of 28 days and assigned, according to initial body weight and the litter of origin, to one of six treatment groups: 0 ppm zinc, 100 ppm zinc; 200 ppm zinc; 1000 ppm zinc; 2500 ppm zinc and 4000 ppm zinc. Diarrhoea was observed only during the first two weeks after weaning. The percentage of piglets with diarrhoea was significantly influenced by the administration of zinc in feed. The results demonstrated that, among the piglets fed with 2500 ppm or 4000 ppm zinc, a significantly lower number of piglets required anti-diarrhoea treatment. However, differences between the 2500 ppm and the 4000 ppm groups were not observed in this respect. If high amounts of zinc were administered for only one week, no differences were observed between treatments, while administration of high levels of zinc during two or three weeks significantly reduced the number of days with diarrhoea per piglet.

[2] Johansen M., Jørgensen L and Schultz M.S., 2007. Effect of zinc and organic acids on diarrhoea in the weaner period. Report no. 778 - link
[3] Hu CH, Song J, Li Y, Luan ZS, Zhu K. 2013a. Diosmectite - zinc oxide composite improves intestinal barrier function, modulates expression of pro-inflammatory cytokines and tight junction protein in early weaned pigs. British Journal of Nutrition 110, p. 681 – 688
[4] Hu CH, Xiao K, Song J, Luan ZS. 2013b. Effects of zinc oxide supported on zeolite on growth performance, intestinal microflora and permeability and cytokines expression of weaned pigs. Animal Feed Science and Technology 181, p. 65 – 71.
[5] Trckova M, Lorencova A, Hazova K, Sramkova Zajacova Z. 2015. Prophylaxis of post-weaning diarrhoea in piglets by zinc oxide and sodium humate. Veterinarni Medicina 60, p. 351 – 360
[6] Hollis G. Use of Growth Promotants in Swine Feeding Programs. National Pork Industry Handbook Fact Sheet N° 31 'Feed Additives for Swine'. 2000
[7] Mateos GG, Garcia Jimenez M, Garcia Lorenzo M. 1998. Composición Micromineral y Vitamínica de Correctores comerciales: Premezclas para porcino. XIV Curso de Especialización. Avances en Nutrición y Alimentación Animal. FEDNA. 1998 - link
[8] Poulsen HD. 1995. Zinc oxide for weanling piglets. Acta Agric. Scand. Sect. A, Animal Sci. 45: 159-167. 1995.

A study to evaluate the effects of adding high amounts of zinc in the diets of weaned pigs (Lima *et al.*, 1994)[9] included 162 piglets from a farm with a previous history of diarrhoea due to *E. coli*. Treatments consisted in a baseline diet of 100 ppm zinc in the form of zinc oxide or the same diet supplemented with 2400 ppm zinc (as zinc oxide). The administration period was 14 or 21 days immediately after weaning. Significant reduction of diarrhoea ($p<0.02$) was observed in animals treated with high zinc diets, although significant differences were not observed between both treatment periods. The conclusion of this study was that adding 2400 ppm zinc (as zinc oxide) for 14 days after weaning reduces the incidence of diarrhoea.

Considering the specific conditions when the products should be recommended, it should be noted that it was not possible to identify a specific target pathogen for zinc oxide and that the published literature supports only the use of zinc oxide in conditions of physiological diarrhoea of the post-weaning period in piglets.

No data from proprietary or published studies are available to support the efficacy of zinc oxide for the treatment of post-weaning diarrhoea in piglets.

Taking into account the overall data available, despite the absence of GCP studies, the CVMP considered that the effect of zinc oxide supplementation on the reduction of post-weaning diarrhoea was considered to be sufficiently substantiated. This effect is limited to prevention of unspecific diarrhoeas occurring at post-weaning period in piglets. The data available shows a beneficial effect of zinc oxide at the dose of 100 mg/kg bw per day (equivalent to 2500 ppm zinc in feed), given in the feed for 12-14 days. Shorter or longer treatment durations were considered not supported by sufficient data.

Concerning the reduction of the use of antibiotics by use of zinc oxide it is considered that the clinical data were too sparse to conclude on this potential effect. No information was available to establish the duration of the effect after the end of zinc oxide administration.

Colistin and zinc oxide combination

Colistin alone is sufficiently effective for the metaphylaxis and treatment of gastrointestinal infections caused by non-invasive *E. coli* (see procedure EMEA/V/A/106)[10]. Considering that the recommended duration of colistin administration in pigs is seven days the concomitant administration of zinc oxide included in the product will also be for seven days. This duration of treatment differs from all other products containing zinc oxide (*i.e.* 14 consecutive days).

The marketing authorisation holder's justification of the combination is based on the addition of the two effects: bactericidal activity of colistin and unspecific protective effect of zinc oxide during the post-weaning period.

The CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005)[11] indicates: 'Any fixed combination product can only be justified, if such a combination offers an advantage over their active substances, when used as single substance products. Fixed combination products cannot be justified for reasons of compensating inadequate diagnosis. Every active substance in a fixed combination should be indicated for use at the moment of treatment and administered in the correct dose.'

No synergy was demonstrated and the potential antagonism was not tested. Moreover the data provided only concern separate use of colistin and zinc oxide and not the clinical use of the

[9] Lima GJM, Mores N, Fialho FB. 1994. Efeito do período de suplementaçao de zinco na dieta sobre o desempenho de suínos desmamados. Vol. 23, no. 6, pp. 949–958, 1994.
[10] CVMP procedure under Article 35 of Directive 2001/82/EC for veterinary medicinal products containing colistin as a sole active substance to be administered orally (Procedure no. EMEA/V/A/106) – link
[11] CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) - link

combination. No study was conducted with the combination in the proposed indication and thus the clinical benefit of the association was not demonstrated.

The proposed indication of the combined product is for treatment, but no clinical data to support the use of zinc oxide in the treatment of diarrhoea (*i.e.* in presence of the disease at the initiation of zinc oxide administration – infection already confirmed in the herd) was available. All data provided for zinc oxide only refer to a prevention claim.

In conclusion, the combination of colistin and zinc oxide for the approved indication (metaphylaxis and treatment of gastrointestinal infections caused by non-invasive *E. coli* sensitive to colistin) for seven days duration of administration is not justified.

Sulfaguanidine and zinc oxide combination

No study was provided to demonstrate the efficacy for the treatment of post-weaning diarrhoeas in piglets. No dose determination study or justification of the selected dose is given, neither confirmatory data supporting an optimal duration of administration of 14 days.

Fixed combination product can only be justified, if such combination offers an advantage over their active substances, when used as single substance products. Advantages of the combination sulfagunidine and zinc oxide versus the use of the individual substances were not provided.

No clinical data was identified to support the claimed indication 'prevention and treatment of various types of diarrhoea occurring at the weaning'. In addition, it appears that zinc oxide is useful to reduce the incidence of post-weaning diarrhoea but not to treat diarrhoea and that it is not possible to clearly identify the mechanism of action of zinc oxide and thus any specific target. The Committee therefore considered that it is not justified to associate an antimicrobial substance (by definition, only appropriate for infectious diseases involving target pathogen(s) and for treatment and metaphylaxis) to zinc oxide because it is not specific-pathogen targeted and has not demonstrated efficacy for treatment. In conclusion the combination of zinc oxide and sulfaguanidine is not justified.

Risks for the environment

A total of five different environmental risk assessments on products containing zinc oxide to be administered orally to piglets for 2-6 weeks, at concentrations ranging between 2500 to 3100 ppm zinc oxide in feed were made available to the CVMP during this referral procedure.

The CVMP considers that four out of five environmental risk assessments have a number of deficiencies on their risk assessment and consequently cannot be used in support of the benefit-risk assessment. Nevertheless, the CVMP would like to note that although these assessments are not considered further, the outcome of two of them also indicate a risk (PEC/PNEC≥1) for the only compartments assessed (soil and surface waters).For the other two, no Phase II data were provided.

Consequently, the CVMP considers that the environmental risk assessment provided during the referral procedure under Article 33(4) of Directive 2001/82/EC for Gutal (EMEA/V/A/108) is scientifically sound and should be used in the benefit-risk evaluation for products containing zinc oxide to be administered orally to food producing species.

Effect assessment

A number of marketing authorisation holders referred to the European Union Risk Assessment Report (EU RAR) on zinc (2010)[12] in their effect assessment. The PNEC values in this report are considered reliable and, hence, are suitable for use in the risk characterisation veterinary medicinal products containing zinc oxide administered orally to food producing animals. However, since the data search for the EU RAR (2010) was completed, more data have become available and were used by some of the

[12] European Union Risk Assessment Report (EU RAR) on zinc (2010) - link

marketing authorisation holders to establish (refine) the PNECs for the relevant environmental compartments. Not all marketing authorisation holders submitted the information that was required to validate the suitability of these additional studies for PNEC refinements. The marketing authorisation holder Huvepharma, however, did provide robust summaries of the additional peer-reviewed studies used in the effect assessment, that were not included in the EU RAR (2010), including a conclusion on the reliability and validity of each study. Consequently, the CVMP considered that the PNECs proposed by the marketing authorisation holder Huvepharma can be used for the characterisation of risks (calculation of risk quotients (RQs)) of veterinary products containing zinc oxide to be used orally in food producing animals.

Exposure: accumulation, bioavailability and model calculation of zinc concentrations in the environment

It is acknowledged that due to the physico-chemical properties of zinc (non-volatile and non-degradable), continual application of manure from treated animals to land under practices of intensive pig breeding will cause a gradual increase in the topsoil zinc concentration, followed by an increase in other relevant compartments, over time. Therefore, it will only be a matter of time before any PNECs are exceeded in these compartments.

A critical consideration in relation to assessing environmental risk of metals is determining their bioavailability. For each compartment (soil, water and sediment), zinc bioavailability is dependent on various biotic and abiotic factors. In the aquatic compartment, zinc bioavailability in water has been predicted using the Metal Bioavailability Assessment Tool (United Kingdom Environment Agency)[13], a user-friendly version of the Biotic Ligand Model, a model that is used to predict the bioavailable metals for different aquatic species (algae, Daphnia and fish) and has been used and well reported in a large number of peer-reviewed studies for zinc, and the data used in the EU RAR on zinc (2010). The Metal Bioavailability Assessment Tool requires fewer data inputs to predict zinc bioavailability in water than the Biotic Ligand Model, and can be used to calculate site-specific PNECs. The Metal Bioavailability Assessment Tool is based on the outputs from the zinc Biotic Ligand Models and the dataset used in the derivation of the Environmental Quality Standard for zinc, and only requires input data for water pH, dissolved organic carbon and dissolved calcium concentration, but does not take into account the presence of other ions that could affect zinc speciation and, hence, bioavailability.

In soil, properties such as pH, organic carbon content, cation exchange capacity, and clay content determine bioavailability in the terrestrial compartment. The bioavailable fraction of zinc in soils is small (<1%). The most important factors in determining bioavailability (and, hence, ecotoxicity) in soils are soil type and the time between the addition of zinc to soil and toxicity testing ('ageing'). For instance, soils contaminated over an extended period of time show reduced toxicity compared to freshly spiked soils. Consequently an 'ageing' factor of 3 has been established and is used in calculating site-specific PNECs. The calculation of site-specific PNECs for Gutal was carried out using an Excel tool soil PNEC calculator (developed by Arche Consulting)[14] which incorporates parameters relevant to determine soil zinc bioavailability, such as pH, organic and clay content, and the cation exchanged capacity.

For sediment systems, since the sediment predicted environmental concentration (PEC) was derived (EU RAR, 2010) there have been significant changes in the way sediment concentrations are determined. It is believed that bioavailability of metals in sediment can be predicted by measuring the acid volatile sulphide (AVS) and the simultaneously extracted metal (SEM) contents of sediments. Other parameters affecting (lowering) zinc bioavailability in sediments are the presence of precipitated mineral phases, e.g. iron (oxy)hydroxides and manganese oxides, as well as the organic matter content in sediments. Zinc binds strongly to AVS and becomes non-bioavailable, which would allow for

[13] Metal bioavailability assessment tool (M-BAT) - link
[14] Arche Consulting Soil PNEC calculator - link

making a correction on the exposure assessment for bioavailability of metals in sediment systems (ECHA 2014)[15]. AVS is produced by bacteria in anoxic sediments. At the time of the zinc EU RAR (2010) there were too few effects or exposure data to be able to account for the effect of these two parameters (AVS/SEM) on zinc bioavailability in sediments. Consequently, bioavailability was not considered for exposure calculations (establishing the PECs), thus leading to a risk assessment that did not account for the bioavailable fraction of zinc but rather for the total zinc concentrations (bioavailable and non-bioavailable). Hence, where an excess of AVS exists and zinc sulfides are formed, the PNEC may be exceeded considerably before any adverse effects are observed. At a site-specific level, PNEC bioavailability corrections in sediment as a result of AVS/SEM content in sediment, can be made if the necessary data are available; however, such data are scarce. Therefore, while soils and surface waters can both be corrected for bioavailability, a correction has not been possible for the calculation of the sediment PECs in this environmental risk assessment.

Given that the VICH and CVMP guidelines[16,17,18] on the Phase II environmental risk assessment of veterinary medicinal products are not primarily developed for inorganic molecules, many of the assumptions and exposure models described in the guidelines are unsuitable for a substance such as zinc. The Committee also considers that variability in soil characteristics (*i.e.* soil types) causes variation in zinc fate and behaviour. The exposure assessment should ideally have addressed this and considered a realistic worst-case situation with respect to the respective receiving environmental compartments. The CVMP considered that the majority of risk assessments provided for concern products showed deficiencies in the fate models used. The marketing authorisation holder Huvepharma presented a pragmatic approach on their exposure assessment on Gutal and considered the results from a model used by EFSA (the Intermediate Dynamic Model for Metal (IDMM) by Monteiro *et al.* (2010))[19] for estimating the environmental exposure from the use of zinc oxide as feed additive.

The IDMM predicts the long-term mass balance of metals, with defined inputs (e.g. veterinary medicinal products usage) and outputs (e.g. crop off-take, ageing), and concludes that zinc will accumulate in soil following continual application of treated manure with acidic sandy soils being most vulnerable as these soils have a tendency to accumulate zinc more rapidly than other type of soils and will also have a higher drainage and run-off of zinc to surface water. There are a number of uncertainties associated with use of the IDMM for predicting the environmental exposure of zinc from use in veterinary medicinal products, such as the effects of hydrology, dissolved organic carbon and metal aging. Additionally, as the model was not made available to the CVMP, the relevance of the default input parameters could not be assessed and the model could not be run using data on specific application rates for zinc. Therefore, exposure using application rates that are considered relevant from the use of zinc containing veterinary medicinal products are calculated from the pre-defined loading rates of the IDMM. Yet, for higher application rates than those reported using the IDMM (EFSA, 2012)[20] extrapolation is required, and the relationship between the zinc loading rate and the PEC values calculated by the IDMM is not linear, which could question the validity of the extrapolated PECs at the highest zinc application rates. Despite these uncertainties, and in the absence of a better alternative, it is considered that the IDMM can be used to gain a reasonable assessment of the risk to the environment posed by the use of Gutal or any other zinc containing veterinary product. Moreover,

[15] ECHA, 2014. Guidance on information requirements and chemical safety assessment. Chapter R.7b:Endpoint specific guidance
[16] VICH GL6: Guideline on Environmental Impact Assessment (EIAS) for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98) – link
[17] VICH GL38: Guideline on Environmental Impact Assessment for Veterinary Medicinal Products Phase II (CVMP/VICH/790/03) – link
[18] CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005) – link
[19] Monteiro SC, Lofts S, Boxall ABA. 2010. Pre-Assessment of Environmental Impact of Zinc and Copper Used in Animal Nutrition. Report to the European Food Safety Authority - link
[20] EFSA Scientific Opinion on safety and efficacy of zinc compounds (E6) as feed additive for all animal species: Zinc oxide, based on a dossier submitted by Grillo Zinkoxid GmbH/EMFEMA - link

validation of the IDMM has been performed by the comparison of model predictions against published monitoring data for zinc applications. Although limited data were available, results show zinc concentrations are predicted accurately in soils but less so in surface waters and sediment. Additionally, as the IDMM has been taken into consideration for the EFSA assessment of zinc exposure, it may also be considered relevant for the assessment of veterinary medicinal products in terms of environmental exposure assessment.

Risk assessment

Based on the data on Gutal, to assess the risk for each compartment following extended application of manure to land, PECs and PNEC values for each FOCUS[21] scenario were compared at three time points (years: 2020, 2040, 2060), using two application rates: application rate of 7 kg zinc ha^{-1} a^{-1} and a lower application rate of 4 kg zinc ha^{-1} a^{-1}. These application rates were chosen as they were the ones reported in the Monteiro *et al.* (2010) study for feed additives containing zinc oxide and do not represent a worst case scenario for veterinary medicinal products containing zinc oxide which would be in the range of 8 kg ha^{-1} a^{-1}. In the terrestrial and aquatic compartments a risk (RQ >1) was found at 4 out of 19 scenarios and at 5 of out 15 scenarios from 2060 onwards, for the worst case and lower application rate, respectively. For two of the FOCUS scenarios (acidic, sandy soils) the RQs are >1 for both loading rates at all time points. A risk was identified for all FOCUS sediment scenarios, at both loading rates and at each time point. The results of the environmental risk assessment for Gutal reflect the conclusion from EFSA on zinc *i.e.* there is a potential environmental concern related to the aquatic compartment (including sediment), with acidic, sandy, well-drained soils being most vulnerable to these processes.

In order to better indicate the risks posed at application rates considered particularly relevant by the use of Gutal of 8.2 kg zinc ha^{-1} y^{-1}, 7.2 kg zinc ha^{-1} a^{-1}, 3.3 kg zinc ha^{-1} a^{-1} and 2.8 kg zinc ha^{-1} a^{-1}, RQs have been extrapolated (linearly) from application rates of 4 and 7 kg zinc ha^{-1} a^{-1}. This linear extrapolation is questionable, since the processes involved are not linear. The information provided indicates that there are errors and these are more pronounced for the sediment compartment and at low loadings. Despite these uncertainties, considering the nature of the active substance, as an inorganic molecule, and the difficulties identified throughout the application procedure in terms of assessing the environmental risk for a compound 'outside' of current CVMP/VICH guidance, it may be accepted that the estimated PEC values extrapolated from the IDMM outputs offer a reasonable reflection of the environmental exposure for use in the risk characterisation for Gutal.

Although the PEC values for each compartment cannot be verified because the IDMM is not provided, overall they appear fairly conservative since a reasonable worst case exposure scenario is considered, *i.e.* continual application of undiluted manure until 2060. Concerning sediment PECs specifically, accumulation factors are not considered (e.g. deposition, re-suspension, and burial of zinc), it is assumed that suspended sediments are representative of the deposited sediment, and no account is made for acid volatile sulfide levels. The latter can reduce zinc bioavailability and, although levels are variable, where zinc sulfides are formed PNECs may be greatly exceeded before adverse effects are observed.

The combination of a conservative PNEC (not accounting for bioavailability) and PEC may result in an overestimate of the risk due to zinc in sediments. The greatest certainty in the IDMM PECs is for the soil compartment, with a lower certainty for surface waters and, then sediments. However, it is apparent that, for all compartments, RQs will be exceeded either immediately (sediment) or eventually (soil, ground-, and surface waters), and these risks must be addressed. As zinc is a metal, general assumptions that are usually made about degradation are not applicable; therefore, once critical concentrations are exceeded, the risk will be difficult to remedy.

[21] Forum for Co-ordination of Pesticide Fate Models and their Use (FOCUS) - link

Overall, it is apparent that the long-term, continual use of zinc-containing veterinary medicinal products will result in a gradual net input of zinc to the environment. No matter which model and application rates are used, a risk to the environment is predicted (RQ ≥ 1), and it will only be a matter of time before risks are present in all environmental compartments if manure from pigs treated with veterinary medicinal products containing zinc oxide is applied to land.

Supporting field studies on zinc accumulation in soils were not available during the referral procedure under Article 33(4) of Directive 2001/82/EC for Gutal (EMEA/V/A/108). For this referral procedure, and to support the risk assessment on zinc from its oral use as a veterinary medicinal product in food producing animals, Bak *et al*. (2015)[22] analysed for a 28 year period following application of pig slurry. The data showed that the use of pig slurry on soils has led to a significant increase in soil concentrations of zinc, especially in the latest period monitored (1998 to 2014). In 45% of all soil samples, PNECs were already exceeded. In sandy soils, PNECs were exceeded in 66% of all cases. It has to be noted that bioavailability was not considered but the PNECs used in this study were higher (less worst-case) than those reported in the EU RAR and that the annual application of manure was based on 140 kg/N/ha/year which is less worst-case than the European limit for sensitive soils of 170 kg/N/ha/year. Besides this, the authors concluded that the current use of zinc in pig production in Denmark may lead to leaching of zinc from fields fertilised with pig slurry into the water compartments, in concentrations that may pose a risk to aquatic species. This Danish national monitoring study confirms the results obtained with the IDMM and CVMP guidelines that the use of veterinary medicinal products containing zinc oxide leads to a significant increase in the soil zinc concentrations (and such is ultimately reflected in water concentrations). Actually, the use of veterinary medicinal products containing zinc oxide contributes to about 30% of the total zinc present in manure. For this 30% contribution alone a risk is already identified for Danish soils.

Risk mitigation measures

Although there are uncertainties with the linear extrapolation of the IDMM results, the PEC values extrapolated from the IDMM outputs are considered to offer a 'reasonable' reflection of the environmental exposure for use in the risk characterisation of veterinary medicinal products containing zinc oxide for use in food producing animals. At present it is uncertain as to what represents a reasonable worst case exposure scenario for the manure application rate. Nonetheless, for each compartment, risks have been identified for some scenarios at each application rate investigated. Considering the use of these products, current EU rules and Good Agricultural Practice on manure spreading, how the target animals are kept and how manure is managed, the suggested risk mitigation measures (dilution of manure and distance to surface waters), although they are in line with the CVMP/VICH guideline (CVMP/VICH/790/03) and were recommended for the referral procedure under Article 33(4) of Directive 2001/82 for Gutal (EMEA/V/A/108), in order to reduce the accumulation of zinc in each compartment, cannot guarantee that they can effectively eliminate either the imminent and future environmental risks identified from the risk assessment, but will just delay the total zinc accumulation in the environment (*i.e.* the time when the PEC will exceed the PNECs). This is not only applicable on farms where dilution of manure is not possible, but also for farms that are able to dilute manure. Although during the aforementioned referral procedure for Gutal, the possibility of not spreading of manure on the same area of land in successive years in order to slow down the accumulation of zinc was considered as a possible risk mitigation measure, and despite being in line with the criteria set out by the CVMP reflection paper on risk mitigation measures[23], it may prove difficult to enact in reality; not only in instances where there may not be the possibility to apply

[22] Bak JL, Jensen J, Larsen MM. 2015. Belysning af kobber- og zinkindholdet I jord. Videnskabelig rapport fra DCE – Nationalt Center for Miljø og Energi – nr. 159. – link

[23] CVMP reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products (EMA/CVMP/ERAWP/409328/2010) - link

treated manure to different areas of land, but also because of the trade on manure between Member States and possibility for manure containing high concentrations of zinc oxide being used in susceptible soil types.

Regarding the risk mitigation measure for compliance with local or national rules for the minimum distance from open water at which manure should be spread, the CVMP considered that this would only be applicable to prevent direct entry to water courses, but would not affect the zinc reaching water surface and drinking water through leaching and run-off processes.

Consequently, the CVMP considers that in the light of overall data available, environmental risks identified by the continuous annual accumulation of zinc in soil from the spreading of manure in agricultural land cannot be effectively controlled through the application of the two risk mitigation measures presented above. The above risk mitigation measures will only delay the risks identified in all environmental compartments if manure from pigs treated with veterinary medicinal products containing zinc oxide is applied to land.

Risks of (co-)selection of resistant bacteria

According to recently published data, zinc used in animal farming might promote the spread of antibiotic resistance due to co-resistance. Several published studies demonstrated (during *in vivo* experiments or by investigating environmental isolates) a correlation between high doses of zinc supplementation in food and the prevalence of antimicrobial resistance. However, the importance of these findings to animal and public health remains unclear due to gaps in the available knowledge.

A reduction in the use of antimicrobials to treat post-weaning diarrhoea in piglets is likely to reduce the selective pressure for antimicrobial resistance development. However, the potential reduction in antimicrobial use secondary to zinc oxide use is not considered to qualify as an 'additional benefit' in this case. The use of zinc oxide may promote the selection of bacteria expressing zinc resistance. The *czrC* zinc resistance gene has been shown to occur on SCCmec of meticillin-resistant *Staphylococcus aureus* (MRSA) and zinc use has been shown to result in co-selection for MRSA carrying this gene (Cavaco *et al.*, 2010)[24]. However, increases in MRSA prevalence during the administration of zinc oxide to piglets appear partly transient (Slifierz *et al*., 2015)[25]. Zinc supplementation may also directly influence the antimicrobial resistance profiles of bacteria via other mechanisms based on work in *E. coli* (Bednortz C. *et al*., 2013)[26]. However, more studies are required to fill remaining data gaps in this area and to confirm these effects.

At this time a detailed risk assessment to examine the risk(s) associated with the co-selection for antimicrobial resistance following the use of zinc oxide is not available. Therefore, in the absence of more data, it is not possible to further characterise the risk posed to both public and animal health. The data presented identify a hazard for human and animal health but, at the present time, that risk is not quantifiable.

[24] Cavaco LM, Hasman H, Stegger M, Andersen PS, Skov R, Fluit AC, Ito T, Aarestrup FM. 2010. Cloning and occurrence of czrC, a gene conferring cadmium and zinc resistance in Methicillin-Resistant *Staphylococcus aureus* CC398 isolates. Antimicrobial Agents and Chemotherapy 54: 3605–3608.
[25] Slifierz MJ, Friendship R, Weese JS. 2015. Zinc oxide therapy increases prevalence and persistence of methicillin-resistant *Staphylococcus aureus* in pigs: A randomized controlled study. Zoonosis and Public Health 62(4): 301-308.
[26] Bednorz C, Oelgeschläger K, Kinnemann B, Hartmann S, Neumann K, Pieper R, Bethe A, Semmler T, Tedin K, Schierack P, Wieler LH, Guenther S. 2013. The broader context of antibiotic resistance: Zinc feed supplementation of piglets increases the proportion of multi-resistant *Escherichia coli* in vivo. International Journal of Medical Microbiology 303(6–7): 396–403.

3. Benefit-risk assessment

Benefit assessment

Direct therapeutic benefits

The data presented support the use of veterinary medicinal product containing zinc oxide for prevention of post-weaning diarrhoea in piglets at the dose of 100 mg/kg bw per day (equivalent to 2500 ppm zinc in feed), for a duration of 14 days. The available data did not include a multicentre GCP field study conducted in several geographical arears Europe and on animals representing the range of various husbandry practices.

Recommended duration of administration

The available information supports the duration of 12 to 14 days for prevention of post-weaning diarrhoea in piglets. It appears that one-week of administration is not sufficiently efficacious and a duration longer than 14 days is not justified either.

Duration of the protective effect

The duration of the protective effect was investigated only in one study (Johansen *et al.* (2007), in which the follow-up period was approximately 41 days. However, after the cessation of zinc oxide supplementation at day 14, acids were added in the feed and consequently the effects of each component could not be evaluated during the follow-up period. Therefore, the continued beneficial effect of zinc oxide after cessation of treatment remains unclear.

Determination of specific conditions

- The aetiology of the observed diarrhoea was not established in most of studies submitted. The specific action (on some pathogens) or unspecific action (local action on the digestive tract) is thus not yet fully elucidated. Thus, it seems that the indication should be limited to the prevention of unspecific diarrhoea of post-weaning *i.e.* induced by the practice of weaning in certain conditions of breeding. Nevertheless there remains the potential risk of overuse of zinc oxide, as it is not possible to predict which animals will develop diarrhoea, as some cases of diarrhoea at weaning are only transitory and slight and without impact on general health of the animals.
- Based on the studies provided, the efficacy of high content of zinc oxide in feed was shown in weaned piglets aged 3-4 weeks old in particular breeding conditions (intensive breeding, housing in building, grouping in pens with piglets of different litters/origins, premature separation with the sow, abrupt feeding transition from milk to cereal based feed). The efficacy in piglets weaned later is not documented neither in less intensive breeding conditions.
- The absence of a multicentre field study conducted through Europe according to GCP to test the efficacy of such products in various field conditions does not permit to define the indication more precise than ‘post-weaning diarrhoea’, neither to conclude on the efficacy of the products in situations where specific pathogen(s) is (are) involved nor in situations other than e.g. weaning piglets at 3-4 weeks of age. It is still difficult at present time to define the situations in which the zinc oxide containing products will be beneficial or not beneficial.

Treatment of post-weaning diarrhoea in piglets

In the absence of data the indication ‘treatment of post-weaning diarrhoea in piglets’ is not supported.

Combination of zinc oxide and colistin or sulfaguanidine

Based on the data presented, the combinations of zinc oxide, recommended for the prevention of unspecific diarrhoea during the post-weaning period, with any antimicrobial substance recommended for treatment and metaphylaxis of diarrhoea induced by target pathogen(s), are not justified.

Additional benefits

Reduction of global use of antibiotics

Zinc oxide has been authorised for several years in a number of EU Member States and experience in some of these countries suggests that zinc oxide use may be correlated with a smaller magnitude of reduction in colistin use than was previously expected, in addition, zinc used in animal farming might have a role to play in increasing the prevalence of antibiotic resistance due to co-resistance.

Scarce data have been presented on the potential effect of using zinc oxide in the reduction of use of antibiotics and therefore no conclusions can be made in this regard.

Risk assessment

Antimicrobial resistance

According to recently published data, zinc used in animal farming might promote the spread of antimicrobial resistance (MRSA) due to co-resistance. Several published studies demonstrated (during *in vivo* experiments or by investigating environmental isolates) a strong correlation between high doses of zinc supplementation in food and an increase in the prevalence of antimicrobial resistant bacteria. It appears that zinc oxide administered at high doses may co-select for antimicrobial resistance, a phenomenon shown *in vivo* for LA-MRSA ST398. However, these effects have only been observed during early treatment.

At this time a detailed risk assessment to examine the risk(s) associated with the co-selection for antimicrobial resistance following the use of zinc oxide is not available. Therefore, in the absence of more data, it is not possible to further characterise the risk posed to both public and animal health. The data presented identify a hazard for human and animal health but, at the present time, that risk is not quantifiable.

Tolerance

A target animal safety study was performed at the recommended dose (100 mg/kg bw per day during 14 days) and no significant side effects have been observed. At higher dose (x3 during 28 days) significant side effects (impact on growth rate, clinical signs) have been observed. The margin of safety can be considered as lower than 3 times the recommended dose.

Environment

Data indicates that the annual application of manure coming from farms where animals are treated with veterinary products containing zinc oxide, results in the gradual and continuous increase of zinc in soil, water and sediment systems. Due to the intrinsic nature of zinc (non-volatile and non-degradable), the potential for PNECs to be eventually surpassed as a result of continual application of manure from treated animals to land over an extended period is a significant environmental concern, particularly with regard to the most vulnerable soil types (acidic, freely draining, sandy soils) and organisms of the aquatic compartments. This increase in zinc concentrations in soil and consequent risks identified for selected compartments is established in this assessment only considering exposure of zinc coming from veterinary products. Potential additional exposure concentrations, e.g., from feed additives containing zinc or other industrial sources, have not been taken into account for this environmental risk assessment. Contamination of soil and water systems by heavy metals, such as zinc, is currently difficult to remedy with existing technologies. The CVMP acknowledges that a fraction

of the zinc added in soil through manure applications will be taken up by plants and can be mineralised and be sequestrated in soil particles and is thus unavailable.

If current practices remain unchanged in the near future, the continual application of manure from treated animals will result in risks (defined by RQ values >1) being established in 4 of 19 soil scenarios, 5 of 15 surface water scenarios and each of the 15 sediment scenarios by 2060. At an earlier time (year 2020) a risk is identified for two of 15 surface water scenarios (acidic, sandy soils) and for all 15 sediment scenarios. However, it is noted that the level of uncertainty in the risk characterisation for sediment is considerably greater than for soil or surface waters given that bioavailability considerations were harder to take into account.

This trend of zinc accumulation on agricultural soils from the veterinary use of zinc oxide has been recently reported by Bak *et al.* (2015). In this report, monitoring data in soil from Denmark showed that the use of pig slurry on soils has led to a significant increase in total soil concentrations of zinc, especially in the latest monitoring period from 1998 to 2014. In 45% of all soil samples, PNECs were already exceeded. In sandy soils, PNECs were exceeded in 66% of all cases. It has to be noted that the PNECs used in this study is adapted to Danish situations and may be lower (more worst-case) in other parts of Europe with different soil types. The authors of the report also concluded that the current use of zinc in pig production in Denmark may lead to leaching of zinc from fields fertilised with pig slurry into the water compartments, in concentrations that may pose a risk to aquatic species.

Risk management or mitigation measures

For all compartments, risks have been identified for some scenarios at the application rates investigated. Considering the use of these products, current EU rules and Good Agricultural Practice (GAP) on manure spreading, how the target animals are kept and how manure is managed, the risk mitigation measures proposed above, although they are in line with the CVMP/VICH guideline (CVMP/VICH/790/03) and were proposed for the referral procedure on Gutal under Article 33(4) of Directive 2001/82/EC (EMEA/V/A/108) in order to reduce the accumulation of zinc in each compartment, cannot guarantee that they can effectively eliminate imminent and future environmental risks identified in the risk assessment, but will just delay the total zinc accumulation in the environment, (*i.e.* the time when PEC will exceed PNECs). This is not only applicable on farms where dilution of manure is not possible, but also for farms that are able to dilute manure. During the aforementioned procedure for Gutal, the possibility of not spreading manure on the same area of land in successive years in order to slow down the accumulation of zinc was considered as a possible risk mitigation measure. Although this is in line with the criteria set out by the CVMP reflection paper on risk mitigation measures, it might be difficult not only in instances where there may not be the possibility to apply treated manure on different areas of land, but also because of the trade on manure between EU Member States and possibility for manure containing high concentrations of zinc oxide being used in susceptible soil types.

Regarding the risk mitigation measure for compliance with local or national rules for the minimum distance from open water at which manure should be spread, the CVMP considered that this would only be applicable to prevent direct entry to water courses, but would not affect the zinc reaching surface water and drinking water by leaching and run-off processes.

Consequently, the CVMP considers that the environmental risks identified by the yearly accumulation of zinc in soil from the spreading of manure in agricultural land cannot be solely controlled with the aforementioned risk mitigation measures. Even applying the risk mitigation measures above it will only be a matter of time before risks are present in all environmental compartments if manure from pigs treated with veterinary medicinal products containing zinc oxide is applied to land.

Evaluation and conclusions on the benefit-risk balance

Zinc oxide is considered to be beneficial for the prevention of post-weaning diarrhoea (*i.e.* reduction in the incidence of diarrhoea during the post-weaning period) in piglets. This beneficial effect of zinc oxide was demonstrated at a dose of 100 mg/kg bw per day (equivalent to 2500 ppm in feed), administered during 12-14 days from weaning.

Curative treatment of post-weaning diarrhoeas in piglets is not supported by data provided.

The margin of safety for the target animals at the dose stated above is relatively small but acceptable.

According to recently published data, zinc used in animal farming might increase the prevalence of antibiotic resistant bacteria due to co-selection for antimicrobial resistance genes. Several published studies demonstrated during *in vivo* experiments or by investigating environmental isolates a correlation between high doses of zinc supplementation in food and the prevalence of antimicrobial resistant bacteria (LA-MRSA) or of multi-resistant bacterial clones (*E. coli*). At this time a detailed risk assessment to examine the risk(s) associated with the co-selection for antimicrobial resistance following the use of zinc oxide is not available. Therefore, in the absence of more data, it is not possible to further characterise the risk posed to both public and animal health. The data presented identify a hazard for human and animal health but, at the present time, that risk is not quantifiable.

Due to accumulation of zinc risks have been identified for all environmental compartments, either immediately (sediment, some soil and surface water types) or delayed (other soil types, ground-, and surface waters). Zinc does not degrade in the environment, and a zinc load in the environment, once established, is difficult to remedy with existing technologies.

The CVMP considers that the environmental risks identified by the yearly accumulation of zinc in soil from the spreading of manure in agricultural land cannot be controlled with risk mitigation measures.

Therefore, the CVMP, during its December 2016 meeting, considered that the overall benefit-risk balance for the veterinary medicinal products containing zinc oxide to be administered orally to food producing species is negative, as the benefits of zinc oxide for the prevention of diarrhoea in pigs do not outweigh the risks for the environment. The Committee acknowledged that there is a risk of co-selection for resistance associated with the use of zinc oxide, but at the present time, that risk is not quantifiable.

4. Re-examination procedure

Following the CVMP opinion of 8 December 2016 on this referral procedure, several marketing authorisation holders (aniMedica GmbH, Huvepharma N.V., DSM Nutritional Products (UK) Ltd., Provimi Ltd., Andrés Pintaluba S.A., Bio Vet Aps, Calier Portugal S.A., Dunavet-B Zrt., Industrial Veterinaria S.A., Laboratorios Calier S.A., Laboratorios Support Pharma S.L., S.C. Crida Pharm S.R.L., ScanVet Animal Health A/S, Sintofarm S.p.A, Tekro, spol. s r.o., Vepidan Aps, Vetlima S.A., Vetoquinol Biowet Sp. z o. o. and Vetpharma Animal Health S.L.) requested a re-examination of the CVMP opinion.

The marketing authorisation holders' grounds for the re-examination were submitted before 6 February 2017.

Some of the grounds for re-examination raised by the marketing authorisation holders related to considerations of a procedural and legal nature. It should be noted that the CVMP is a scientific Committee and that while it operates within the framework of the Union legislation regulating veterinary medicinal products, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations

are not within the remit of the CVMP; therefore during the re-examination of the present referral procedure the CVMP considered only the marketing authorisation holders' scientific grounds for re-examination.

The Committee's conclusions on the points raised in the marketing authorisation holders' scientific grounds are given below.

aniMedica GmbH

aniMedica's scientific grounds for re-examination focused on benefits associated with the use of their products (veterinary medicinal products containing colistin sulfate and zinc oxide), risks for (co-)selection of resistance genes and risks for the environment associated with the use their products.

The posology of aniMedica's veterinary medicinal products (daily dose of 1 g product per 5 kg bw, equivalent to 5 mg colistin sulphate and 96 mg zinc oxide per kg bw, for 5 – 7 days), means that the concentration of zinc oxide in-feed will be 3000 ppm (approximately 2400 ppm zinc). The CVMP confirmed that, at this level, zinc oxide cannot be considered as an excipient only and that furthermore, considering the substantial amount of zinc oxide present in the aforementioned products (Enteroxid N AMV aniMedica and aniMedica Enteroxid N), the classification of the substance as an excipient or active substance is not relevant. Also, piglets are weaned between 3-4 weeks of age (i.e. 7-8 kg), but the claim for the aforementioned products is for pigs up to 40 kg bw. The clinical relevance of zinc oxide in reducing the level of *E. coli* diarrhoea for these heavier pigs is unknown. The Committee considered that colistin mono-product alone would be sufficient to reduce clinical diarrhoea, when used for seven days in close connection to weaning, where *E. coli* diarrhoea is the primary cause of diarrhoea. It should be noted that no information supporting a seven days administration of zinc oxide was available. In the trials with only seven days of zinc oxide supplementation at the recommended dose no significant effect was shown.

The CVMP considered that the combinations of zinc oxide, recommended for the prevention of nonspecific diarrhoea during the post-weaning period, with any antimicrobial substance recommended for treatment and metaphylaxis of diarrhoea induced by target pathogen(s), are not justified.

The marketing authorisation holder states that concerns for antimicrobial resistance related to high dose zinc oxide do not apply to their products, and most concerns are hypothetical. The CVMP does not accept these arguments, where the marketing authorisation holder's products have the same proportional risk for selecting antimicrobial resistant bacteria as zinc oxide mono-products.

The CVMP cannot support the claim by the marketing authorisation holder stating that determining the environmental risks should be based on consideration of the conditions in Germany only, as the products are nationally authorised in this Member State only. The CVMP considers that because Enteroxid products are included within the scope of this procedure under Article 35 of Directive 2001/82/EC for veterinary medicinal products containing zinc oxide to be administered orally to food producing species, such argument is not applicable. The marketing authorisation holder concludes that the amount of zinc oxide released to the environment from the use of these products in Germany is significantly lower than that from other concerned products, and below established annual loads allowed for environmental release of zinc in Germany. However, while the marketing authorisation holder claims a lower exposure and annual load from their products compared to other zinc oxide veterinary medicines, they have not submitted data supporting a quantitative risk assessment, and have not considered that, while their conclusion on a limited environmental release of zinc oxide was estimated from the use of these products on 3-4 week old piglets (7-8 kg), the claim for their products is for pigs up to 40 kg/bw, and treating heavier pigs would also increase the environmental load. As a result, the CVMP considers that the environmental risk assessment presented above for all zinc oxide

mono-products is also adequate to predict environmental risks from the use of Enteroxid products in the EU.

Huvepharma N.V.

Huvepharma's scientific grounds for re-examination focused on risks for the environment. The CVMP does not agree with the marketing authorisation holder's argument that the initial benefit-risk assessment was concluded to be positive for the procedure under Article 33(4) of Directive 2001/82 for Gutal (EMEA/V/A/108). During the above-mentioned referral procedure, a complete benefit-risk assessment was not conducted by the CVMP, and while the therapeutic benefits of Gutal were not taken into account as the product is a generic and bioequivalence with the reference product was accepted, quality, target animal safety, user safety impact on antimicrobial resistance development and residues were not assessed during the initial referral procedure, (given the scope of that referral).

For the grounds of re-examination, the marketing authorisation holder focuses on what they believe to be inconclusive results from a recent Danish soil monitoring study (Bak *et al.* 2015). The CVMP agrees that this study cannot be used, on its own, as proof that environmental risks exist from the use of zinc oxide in pig production. However, the study supports the line of evidence that the use of zinc oxide as a veterinary medicinal product in pig farming will lead to a gradual accumulation in agricultural soils, which will eventually not only exceed safe concentrations of zinc in soil, but also in sediment and water systems. The marketing authorisation holder also chose to include bioavailability aspects in soil by calculating $PNEC_{bioavailable}$ for 19 European soils by means of the Arche Soil PNEC calculator. However, the CVMP was not able to establish the validity of the PNEC values reported as the Arche Soil PNEC calculator and the set of relevant input parameters was not made available to the CVMP during the initial assessment. The CVMP recognises the importance of bioavailability when addressing toxicity of metals, and considers that while different models might take into consideration the bioavailable fraction of zinc oxide and conclude on a slight different timeframe for when (i.e., in which year) environmental risks are predicted to occur, none of the models support a prediction of no environmental risk from the use of zinc oxide as a veterinary medicinal product, nor that zinc in soil will not become bioavailable to soil, water or aquatic biota.

The marketing authorisation holder also argues the lack of justification for rejecting risk mitigation measures proposed during the procedure under Article 33(4) of Directive 2001/82 for Gutal (EMEA/V/A/108). The CVMP notes that after further considerations regarding the current EU rules and Good Agricultural Practice on manure spreading, and how the target animals are kept and how manure is be managed, the initially suggested risk mitigation measures would slow down the accumulation of zinc in each compartment. However, this would just delay the total zinc accumulation in the environment (*i.e.* the time when PEC will exceed PNECs), but given the nature of zinc risk mitigation measures cannot guarantee that they can effectively eliminate short term (2020) risks identified in the risk assessment. During the aforementioned referral procedure for Gutal, the possibility of not spreading of manure on the same area of land in successive years in order to slow down the accumulation of zinc was considered as a possible risk mitigation measure. Although this risk mitigation measure could be considered in line with the criteria set out by the CVMP reflection paper on risk mitigation measures (EMA/CVMP/ERAWP/409328/2010), the CVMP was of the view that, in practice, applying this risk mitigation measure will not be feasible where there may not be the possibility to apply treated manure on different areas of land or where there is trading of manure. There is also the possibility for manure containing high concentrations of zinc oxide being applied to susceptible soil types. Regarding the potential for risk reduction when complying with local or national rules for the minimum distance from open water at which manure should be spread, the CVMP considered that this would only be applicable to limit direct entry to water courses, but would not affect the zinc reaching water surface by leaching and run-off processes. Consequently, the CVMP considers that the previously recommended risk mitigation measures within the scope of procedure under Article

33(4) of Directive 2001/82 for Gutal (EMEA/V/A/108), will only delay the risks identified in all environmental compartments if manure from pigs treated with veterinary medicinal products containing zinc oxide is applied to land.

DSM Nutritional Products (UK) Ltd. and Provimi Ltd.

The marketing authorisation holders informed the EMA that they had not received the official notification of the inclusion of their products (Pigzin and ZincoTec) in this Article 35 referral procedure. Therefore the information submitted by those marketing authorisation holders at the stage of re-examination was taken into consideration in order to safeguard their rights.

DSM Nutritional Products and Provimi's scientific grounds for re-examination focused on efficacy of zinc oxide, risks for (co-)selection of resistance genes and risks for the environment.

No original proprietary data or clinical trials were submitted by the marketing authorisation holders in support of the indications and dose. Much of the text was focused on the health and growth benefits of zinc oxide. However, the only authorised indications are for the treatment and control of diarrhoea in piglets. Several of the publications submitted in support of the dose were not relevant since the investigations either focused on the growth benefits of zinc oxide or clinical trials combining both zinc oxide and antimicrobials. This restricts the focus to the findings of Poulsen (1995), and Holm (1990)[27]. In some of the other trials, no diarrhoea was observed in the piglet groups. Overall, of the bibliographic references provided by the marketing authorisation holders there were issues with the study designs that preclude support of 2500 ppm zinc oxide in feed for 14 days post-weaning as described in the approved indications. No studies were submitted to support the treatment indication. To conclude on this point, the marketing authorisation holders did not provide any additional data that will change the original CVMP conclusion with regard to efficacy. That is, notwithstanding the deficiency in the data presented it is considered that the efficacy of veterinary medicinal products containing zinc oxide for prevention of post-weaning diarrhoea in piglets is demonstrated.

The CVMP acknowledges that LA-MRSA is a rare cause of infection in pigs, but an emerging public health concern due to the high carrier status in pigs and the transference of MRSA to food products and in-contact humans (e.g. pig farmers, veterinarians, slaughter house employees). The fact that LA-MRSA CC398 has currently a low impact on human populations does not negate the public health concerns.

With regard to environmental risks, the marketing authorisation holders consider that in the initial assessment the CVMP did not use the risk assessment methodology applied during the EU RAR on zinc, and argues that the developments in the scientific literature published after the EU RAR on zinc, on how to incorporate metal bioavailability in the a risk assessment, were not taken into consideration.

The marketing authorisation holders presented an environmental risk assessment by: a) addressing measured soil concentrations of zinc in (Danish) soils - but not taking into consideration the contributing from the repeated (annual) load of zinc from non-aged pig slurry; and b) by combining two methods for incorporating bioavailability (the so called 'added risk approach' together with the 'bioavailability correction approach'), yet the combination of both is not supported by the CVMP. The CVMP has calculated PEC_{soils} when taking into account the two approaches noted above, separately. The results indicate that for both clay and sandy soils a risk is identified using added-risk approach, with PEC values being above the $PNEC_{soil}$ of 26 mg/kg. On the other hand, using the bioavailability correction approach, and considering within this approach that bioavailability is dependent on soil type and the time zinc was incorporated onto soil (i.e., zinc aging), the bioavailable fraction was for both

[27] Holm, A. (1990) *E. coli* associated diarrhoea in weaner pigs: zink oxide added to the feed as a preventive measure. Proceedings of the International Pig Veterinary Society Congress, Lausanne, Switzerland, p154.

clay and sandy soils below the $PNEC_{soil}$ of 26 mg/kg (16.3 and 14.4 mg/kg for sandy and clay soils, respectively).

Regardless of the approach presented, data indicates that if the uses of zinc oxide as a veterinary medicinal product in pig farming, and applications of manure to land continue as they have been in the last years, zinc will continue to accumulate within the soil matrix, leading to an increase in bioavailable fraction of zinc in soils, eventually to levels higher than the PNEC.

The CVMP concluded that when using the added risk approach, then:

- A risk of zinc to soil dwelling species is already present in clay soil;
- A risk of zinc to soil dwelling species is already present in sandy soil.

And when using the bioavailability correction, then:

- A risk of zinc to soil dwelling species will on average be reached in approximately 55 years in clay soils;
- A risk of zinc to soil dwelling species will on average be reached in approximately 31 years in sandy soils.

To manage the risks and determine adequate risk mitigation measures, the marketing authorisation holders suggest adding a number of statements on the product information regarding the mixing and/or spreading of manure to land. However, and as noted above, the previously suggested risk mitigation measures would slow down the accumulation of zinc in each compartment, thus just delaying the total zinc accumulation in the environment (*i.e.* the time when PEC will exceed PNECs), but given the nature of zinc they cannot guarantee that they can effectively eliminate imminent and future environmental risks identified in the risk assessment.

Andrés Pintaluba S.A., Bio Vet Aps, Calier Portugal S.A., Dunavet-B Zrt., Industrial Veterinaria S.A., Laboratorios Calier S.A., Laboratorios Support Pharma S.L., S.C. Crida Pharm S.R.L., ScanVet Animal Health A/S, Sintofarm S.p.A, Tekro, spol. s r.o., Vepidan Aps, Vetlima S.A., Vetoquinol Biowet Sp. z o. o. and Vetpharma Animal Health S.L.

The marketing authorisation holders' grounds for requesting a re-examination of the CVMP opinion focused on risks for (co-)selection of resistance genes and risks for the environment.

While the marketing authorisation holders acknowledge possible links between zinc oxide veterinary medicinal products to multi-resistant bacteria (e.g. LA-MRSA, *E. coli*) and the environment, the marketing authorisation holders regard that the benefits of their products outweigh the risks. They further state that their products contribute to achieving lower antimicrobial consumption in pigs, and that the identified risks will not be mitigated by removing veterinary medicinal products containing zinc oxide from the market. The marketing authorisation holders, while acknowledging that there is a risk to the environment due to accumulation of zinc, are proposing to collect data on the sale and consumption of veterinary medicinal products containing zinc oxide within the ESVAC activity, as it is already done with antibiotics, as such data would help to further investigate the use and consequent environmental impact of zinc oxide when used as a veterinary medicinal product. Additionally the marketing authorisation holders consider that an ad hoc expert group together EFSA could help to address the environmental risks from a broader point of view.

The Committee accepts that, while there may be a benefit in monitoring the zinc oxide consumption as a veterinary medicine, a risk to the environment has been identified and, at this time, the risks are considered to outweigh the benefits for zinc oxide as a veterinary medicine. Indeed, there are examples that some EU Member States already monitor veterinary medicinal products containing zinc oxide consumption (e.g., Denmark, Czech Republic), as well as zinc soil concentrations (e.g., Denmark).

The marketing authorisation holders accept that, based on the CVMP assessment, the risk mitigation measures proposed will only dilute and not decrease the total zinc output to the environment, and thus it will only be a matter of time before risks are present in all compartments. However, the marketing authorisation holders argue that additional risk mitigation measures could be considered to reduce or limit emission of zinc oxide to the environment from the use of pig manure, but did not propose any additional risk mitigation measures.

The CVMP also notes that other sources of zinc in the environment will also contribute to the yearly increase of zinc oxide to agricultural land.

CVMP overall conclusions after re-examination

Based on the totality of the data available, including the information submitted during the original assessment procedure and the detailed scientific grounds for re-examination put forward by the marketing authorisation holders, the CVMP concluded that there were not sufficient scientific grounds to revise its previous conclusions as included in its opinion of 8 December 2016, which concluded that the overall benefit-risk balance for the veterinary medicinal products containing zinc oxide to be administered orally to food producing species is negative.

Grounds for the refusal of the marketing authorisations and for withdrawal of the existing marketing authorisations

Whereas

- the CVMP considered that based on the available data the efficacy of veterinary medicinal products containing zinc oxide for prevention of post-weaning diarrhoea in piglets is demonstrated;
- the CVMP considered that the efficacy of veterinary medicinal products containing zinc oxide for treatment of post-weaning diarrhoea in piglets is not supported by data and cannot be demonstrated;
- the CVMP considered that based on the available data the clinical benefit of the veterinary medicinal products containing colistin sulfate and zinc oxide cannot be demonstrated;
- the CVMP considered that based on the available data the combination of zinc oxide, for the prevention of unspecific diarrhoea during the post-weaning period, with sulfaguanidine, for treatment and metaphylaxis of diarrhoea induced by target pathogen(s), is not justified;
- the CVMP acknowledged that there is a risk of co-selection for resistance associated with the use of zinc oxide, but at the present time, that risk is not quantifiable;
- the CVMP considered that based on the available data risks to the environment have been identified, due to accumulation of zinc, for all scenarios, either immediately (sediment, some soil and surface water types) or delayed (other soil types, ground-, and surface waters); the CVMP acknowledged that all predictive models have an inherent degree of uncertainty in their parameterisation, and the results generated (i.e., time estimates) are based on a limited amount of input data which is likely to influence the model output;
- the CVMP considered that risk mitigation measures will only dilute and not decrease the total zinc emission output to the environment, and thus it will only be a matter of time before risks are present in all compartments;
- the CVMP considered that the overall benefit-risk balance for the for veterinary medicinal products containing zinc oxide to be administered orally to food producing species is negative, as the benefits of zinc oxide for the prevention of diarrhoea in pigs do not outweigh the risks for the environment;

the CVMP has recommended the refusal of the granting of the marketing authorisations and the withdrawal of the existing marketing authorisations for veterinary medicinal products containing zinc oxide to be administered orally to food producing species as referred in Annex I.