I. SCIENTIFIC OVERVIEW

Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle is an aerosol spray indicated for cattle, sheep and pigs for the prevention of infections of superficial traumatic or surgical wounds caused by microorganisms sensitive to chlortetracycline. The product can be used as part of a treatment for superficial claw/hoof infections, in particular interdigital dermatitis (foot rot) in sheep and digital dermatitis in cattle.

Chlortetracycline hydrochloride has a well-established use in veterinary medicine. Because of this, a company wishing to market a product containing chlortetracycline hydrochloride for use in cattle, sheep and pigs may fulfil the safety and efficacy requirements for a marketing authorisation by submitting a dossier of relevant published literature on such usage, and supplementing this with new information to fill any gaps in the published literature, as well as demonstrating that the published literature is directly relevant to their own product. This is the approach which was taken by Eurovet Animal Health when applying for a marketing authorisation for Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle. This type of application is known as a bibliographic application.

Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle consists of chlortetracycline hydrochloride as a cutaneous spray/suspension. It is supplied in 270 ml and 520 ml pressurised containers. When administering the product the container should be held 15-20 cm from the area to be sprayed for approximately 3 seconds (equivalent to approximately 3.9 g of product or 0.10 g chlortetracycline) until the treatment area is evenly coloured.

II. QUALITY ASPECTS

A Composition

The product is an aerosol for cutaneous use. The amount of active ingredient, (chlortetracycline hydrochloride), present per container equates to 2.45%w/w). Chlortetracycline hydrochloride is not sufficiently soluble in isopropanol to completely dissolve. Therefore the aerosol is a suspension of the active substance in the vehicle propellant. This active substance is combined with a number of excipients: patent blue V, colloidal anhydrous silica, isopropyl alcohol, sorbitan trioleate and butane.

The packaging is a standard non-metered aerosol consisting of a coated tin-plate canister, plastic valve mechanism and spray nozzle nebuliser. The valve mechanism contains a glass marble. The applicant states that the stability data confirm that there is a physical compatibility between the pack materials and the formulation. They also indicate that there is no leaking or obstruction to product flow or discharge.

B Method of Preparation of the Product

The product is manufactured in accordance with Good Manufacturing Practice and, where applicable, conditions, equipment and materials are sterile. The manufacturing formula for a batch size of 1680 kg was provided. This was in agreement with the stated composition for a single canister and included the 13% overage of chlortetracycline hydrochloride.

The suspended active substance, including the dye, sorbitan trioleate and colloidal silica is prepared by high speed mixing. The appearance and relative density of the substance are checked by in-process controls. The canisters are filled by weight and then the valve is installed. The butane is then filled to the required weight under high pressure through the valve. The spray

nozzle and plastic cap are then fitted. A process validation has been performed which comprises a significant amount of filling weight data and particle size analyses.

C Control of Starting Materials

The chlortetracycline hydrochloride used complies with the European Pharmacopoeia monograph. All excipients, with the exception of butane and patent blue V also comply with European Pharmacopoeial monographs. The butane has specifications that have been included for the following parameters: pressure, density, moisture and impurities. In the absence of a European Pharmacopoeial monograph for the colouring agent patent blue V, the material complies with manufacturing specification and the requirements of the French Pharmacopoeia.

The canister is coated with a protective lacquer for which a safety declaration that it is suitable for use in food contact situations has been provided. The glass marble and spray nozzle are also both considered acceptable.

D Specific Measures Concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

All components of the product have been demonstrated to comply with relevant guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicines.

E Control Tests during Production

Control tests on the intermediate products are not applicable as the manufacturing process is continuous.

F Control Tests of the Finished Product

A number of parameters are controlled immediately after the product is manufactured. These include the appearance, identity and content of active ingredients, odour, net fill weight, particle size distribution, pressure test, leakage test, delivery weight, re-suspendability and microbiological content. Data have been provided which indicate the suitability of the methods used in testing the finished product.

G Stability

Active substance

A certificate of suitability of the compliance of the chlortetracycline hydrochloride with the European Pharmacopoeial monograph has been provided. Stability data up to 4 years for three industrial scale batches stored in simulated commercial packaging have also been provided. These data support the four year re-test interval.

Finished Product

The company provided data on three batches of product of production scale. In the case of one batch, these data extended up to 36 months stored at 25°C/60%RH (both in an upright and inverted position), and to 24 months at 40°C/75%RH. Data were provided on parameters likely to be subject to change on storage, including particle size of the active substance, leak testing and re-suspendability. On the basis of these data the proposed 3 year shelf life with no additional storage conditions to those specific to the product and aerosols (i.e. not to expose to sunlight, or occasional exposure to elevated temperatures of 50˚C or more, sources of ignition and freezing conditions) is fully justified.

CONCLUSIONS ON QUALITY

The data provided by the company included satisfactory descriptions of the production and quality control procedures. The finished product tests ensure an efficacious, safe and consistent product. The stability data provided show that a shelf-life of 3 years is justified subject to the correct storage conditions.

Do not refrigerate or freeze Protect from frost Pressurized container. Do not expose the container to direct sunlight or to temperatures higher than 50°C. Keep away from sources of ignition

III. SAFETY ASSESSMENT

Introduction
Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle is an aerosol spray indicated for the prevention of infections of superficial traumatic or surgical wounds caused by microorganisms sensitive to chlortetracycline. The product can be used as part of a treatment for superficial claw/hoof infections, in particular interdigital dermatitis (foot rot) in sheep and digital dermatitis in cattle.

The applicant has noted that powder formulations containing chlortetracycline are currently authorised in the UK for topical use in small and large animals for controlling infections in wounds and that they have been in use for more than 10 years in this country.

Much of the evidence provided by the applicant relates to oxytetracycline and also to some extent tetracycline. This is because there are limited published data available on chlortetracycline itself. However, the applicant has made the case that data on the antimicrobial spectrum and activity of these other tetracyclines are relevant. It is widely accepted that the spectrum of activity of both chlortetracycline and tetracycline is comparable to that of oxytetracycline.

Pharmacological Studies
The applicant has provided brief details with respect to the pharmacodynamics and pharmacokinetics of chlortetracycline. This is considered acceptable given the nature of the product and the intended route of administration. The product will be used to treat wounds on single occasions. Chlortetracycline is poorly absorbed dermally and therefore systemic exposure will be extremely limited.

Toxicological Studies
As indicated in part I of this document, chlortetracycline hydrochloride, the active ingredient in Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle, has a well-established use in veterinary medicine. The safety information submitted by the company includes a review of published literature on the pharmacology and toxicology of chlortetracycline hydrochloride in the prevention of infections of superficial traumatic or surgical wounds caused by microorganisms sensitive to chlortetracycline.

The applicant has provided published studies relating to single dose and repeat dose toxicity. The published single dose toxicity study shows low acute toxicity in mice by subcutaneous and oral

routes. The published studies relating to repeated oral dose toxicity show that the NOEL[1] for oral administration of chlortetracycline in rats was 0.01% in the diet.

Reproductive toxicity, including teratogenicity.
A number of published studies were provided. In one study groups of pregnant mice and rats were orally administered the tetracycline based active ingredient, oxytetracycline between days 6 and 15 of gestation. The results of the study demonstrated that oxytetracycline at doses in excess of those used therapeutically in humans produced maternal and foetal toxicity, mainly observed as decreases in weight gains. There was no evidence of teratogenic action of oxytetracyline.

Mutagenicity
A published study was provided in which oxytetracycline was tested for mutagenicity with the Ames test[2]. Even though chlortetracycline was not tested the tetracyclines were represented by oxytetracycline. Oxytetracycline was not mutagenic in the test but the product of the nitrosation[3] of oxytetracycline was positive in the tests.

Another published study was provided whereby oxytetracycline hydrochloride was tested for mutagenicity. Oxyteracyline hydrochloride, potassium nitrile and a combination of antibiotic and nitrile were tested for mutagenicity in mice. Oxytetracycline hydrochloride by itself was not mutagenetic for the strain of bacteria tested. The combination of the compounds administered in the highest tolerated doses proved to be mutagenic for the strain of bacteria tested.

Carcinogenicity
A published study was provided whereby carcinogenicity of oxytetracycline hydrochloride was investigated in rats and mice. Doses up to 0.5 mg/kg were administered in rats, and 1.25 mg/kg in mice, in the diet for 103 weeks. In male and female rats, tumours were observed in the control group (this group received doses containing no active ingredient), the low dose and the high dose groups. No tumours were observed in the mouse study.

A similar published study was provided whereby carcinogenicity of tetracycline hydrochloride was investigated in rats and mice. Tetracycline hydrochloride was non carcinogenic in both sexes of both species in the dietary feeding studies of 103 weeks duration.

User Safety
The applicant has included the following user safety warnings in the SPC and product literature:

Because of the risk of sensitisation and contact dermatitis, skin contact should be avoided.
Wear appropriate impermeable gloves whilst handling the product.
Because of the risk of eye irritation, contact with the eyes should be avoided. Protect the eyes and face.
Do not spray on a naked flame or any incandescent material.
Do not pierce or burn, even after use.
Avoid inhaling vapours. Apply the product in open air or in sufficiently ventilated area.
Wash hands after use
Do not eat or smoke whilst administering the product.

[1] NOEL = No observed effect level. This is the highest tested dose of a substance that has been reported to have no harmful (adverse) health effects on people or animals.
[2] The **Ames test** is a biological assay to assess the mutagenic potential of chemical compounds.
[3] **Nitrosation** is a process of converting organic compounds into nitroso compounds

The applicant confirms that Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle has been evaluated for toxicity in rats in a 4 hour exposure inhalation toxicity study. It is concluded that the acute inhalation toxicity of the product in rats is low. Therefore, the user safety warnings are considered appropriate for a product of this type.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. This application has been submitted as a bibliographic application and is therefore exempt from the ecotoxicity requirement. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

Residues Documentation

The company presented the results of residue depletion studies following a single cutaneous application of chorotetracycline spray to cows and sheep. The studies were GLP[4] compliant and measured plasma and milk drug concentrations of chlortetracycline (Cyclo Spray) in dairy cows, and plasma drug concentrations in sheep after a single cutaneous application. Blood samples were taken prior to the application and then at a number of time points post-application. Milk samples from cows were also collected before and at 3 successive milkings post-application. The results of the study indicated that between 0 and 48 hours after treatment the levels of Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle in the plasma were below the level of quantification. It was concluded that a zero withdrawal period[5] is appropriate for meat and milk in lactating cows, and for meat in sheep.

MRL

Chlortetracycline is entered into Annex I of Council Regulation (EEC) No 2377/90. The marker substance is the sum of parent drug and its 4-epimer.

Target Tissue	All food producing species MRL's
Muscle	100μg/kg
Liver	300μg/kg
Kidney	600μg/kg
Milk	100μg/kg

Withdrawal Periods

Based on the data provided above the following withdrawal periods are justified.

Sheep (meat) 0 days
Pig (meat) 0 days
Cattle (meat) 0 days
Milk 0 days

CONCLUSIONS ON SAFETY AND RESIDUES

The results of the residue depletion studies in cattle and sheep indicate that absorption of chlortetracycline is negligible following topical application of Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle to compromised skin. The levels of chlrortetracycline present in the plasma are low following topical application. Therefore,

[4] GLP = Good Laboratory Practice

[5] The withdrawal period is the period that must elapse between the time when an animal is last given the product and the time when that animal may be killed for human consumption.

the proposed zero withdrawal periods for meat and milk are considered appropriate to ensure consumer safety.

The applicant has agreed to the following wording on the SPC and label:

Stained part of the pigskin must be removed prior to the rest of the animal being used for human consumption

IV. CLINICAL ASSESSMENT (EFFICACY)

Pre-clinical studies
The pre-clinical data provided in the dossier are mostly derived from published literature. Since the active ingredient has a well-established medicinal use, this is deemed acceptable.
The basic pharmacodynamic data are appropriate, although it was noted that most of the information was either of a general nature or derived from studies with other tetracycline, notably oxytetracycline. The applicant has presented the case that most tetracyclines have a similar spectrum of activity and similar potency.

Tolerance in the Target Species of Animals
The company submitted three studies, which were carried out as part of clinical trails, to investigate whether the product was well tolerated in cattle, sheep and in pigs. The sheep study was carried out in animals with foot rot. Treatment was carried out on day 1 only and consisted of spraying the feet with Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle after the hooves had been prepared and washed. The spray was applied for 3 seconds and after a 30 second interval the animals were retreated with a further 3-second spray. The cattle study was carried out in animals with acute digital dermatitis. In this study the hooves were prepared as in the sheep study and sprayed twice for 3 seconds with a 30 second interval between. This procedure was repeated on three consecutive days. The third trial involved the treatment of piglets with Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle following castration. In this study the spray was applied for 3 seconds on a single occasion. It was reported that no adverse effects (local or systemic) were observed in any of the treated animals and concluded that Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle was well tolerated.

It was acknowledged that allergic reactions to tetracyclines do occur, but are rarely reported after cutaneous administration of these antibiotics.

The applicant noted that it was normal to evaluate the effects of over-dosage and increased duration of treatment. However, it was accepted that applying more spray on a single occasion will simply lead to excess material running off and so over-dosage cannot be realistically evaluated.

Resistance
No specific data have been submitted for chlortetracycline, but an organism resistant to one tetracycline would almost certainly be resistant also to other antibiotics in the same group. Tetracycline sprays have been in use for many years and they are still very popular and widely used. It seems likely, therefore, that resistance is not a serious practical problem with these products and that they remain clinically effective.

Clinical documentation
Since there are few articles in the published literature on the efficacy of a topical application of chlortetracycline for the treatment and prevention of cutaneous infections, much reliance has been

placed on articles reporting work with products containing oxtetracycline. As previously noted the applicant has argued that this is justified in view of the close similarity of these two tetracyclines. In addition to the published data the applicant has conducted clinical trials with Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle These clinical studies were carried out in accordance with GCP[6]. A number of indications in the three target species were examined.

Interdigital dermatitis in sheep (foot rot)
Published literature was provided covering clinical trials on foot rot treatments. In addition to this the applicant conducted a confirmatory clinical trial in sheep treated with Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle. Full details of the trial procedures were provided. It was concluded that treatment of foot rot in sheep with Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle using the recommended posology resulted in a significant improvement in the treated animals in comparison with the untreated group.

Digital dermatitis in cattle
The applicant provided published literature indicating that cutaneous application of oxytetracycline was an effective treatment for digital dermatitis in cattle.
In addition a clinical study was conducted. Results revealed that improvements were seen with Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle in the study, although statistically these were not significant in comparison to the placebo for most parameters, the distinct difference between the groups could be argued to be of clinical significance. These findings, in addition to published data on the beneficial effects of oxytetracycline sprays in treating digital dermatitis in cattle suggest that a claim for the product in this respect is justified.

Primary and Secondary Skin Lesions
A small amount of clinical data taken from published literature was presented. A study was also carried out in groups of castrated pigs. One group were treated topically with Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle, the other group were treated with a placebo spray (one without the presence of chlortetracycline.) The results were in favour of Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle over the placebo spray used.

CONCLUSIONS ON EFFICACY ASPECTS

The evidence provided by the applicant indicates that Cyclo Spray, Chlortetracycline HCl 2.45 % w/w, cutaneous spray, suspension for pigs, sheep and cattle will be effective for the main indications proposed in the SPC and product literature and that it will be safe to use.

V. OVERALL CONCLUSION AND BENEFIT – RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for man and the environment is acceptable.

[6] GCP=Good Clinical Practice

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)