I. INTRODUCTION

The product is a premix for medicated feed containing 25 % chlortetracycline hydrochloride and consists of yellow free flowing granules. The application for this product was submitted as a full national application with a generic basis in accordance with Article 12.3 of Directive 2001/82/EC as amended by 2004/28/EC. This product is a line extension from the product Aurofac 100 Granular, which has 10 % chlortetracycline hydrochloride.

Aurofac 250 mg/g Granular Premix for Medicated Feeding Stuff is authorised for use in pigs, chickens, turkeys and ducks for the treatment and control of respiratory and systemic infections associated with organisms sensitive to chlortetracycline. The dose rate for pigs is 10-20 mg/kg bodyweight daily, for broilers is 20-30 mg/kg bodyweight daily, and for turkeys and ducks it is 10-30 mg/kg bodyweight daily.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

Product Development and Composition

The product contains chlortetracycline hydrochloride and excipients carmellose sodium and calcium sulphate dihydrate. The proposed pack comprises a double layer, low-density polyethylene bag available in capacities of 2, 3, 4.8, 6.4, 8, 9, 12, 16, 20 and 25 kg. The inner layer is opaque white and any printing is applied to the outer layer. Secondary packs constructed from cardboard are also available, containing either 12 x 2 kg or 8 x 3 kg. The particulars of the containers and controls performed are provided and conform to appropriate guidelines. The choice of the formulation is justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

There are no materials that fall within the scope of the TSE guideline are used in the manufacture of the active substance, excipients or in final product manufacturing. This is supplemented by a declaration from the active substance manufacturer stating the manufacturing process is free from materials of animal origin. A full TSE declaration and accompanying format table have been provided.

Active Substance

The active substance is chlortetracycline hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur.). Batch analysis data are presented for five production batches of 1000 kg. These batches have been tested against the European Pharmacopoeia monograph as well as the additional tests specified on the certificate of suitability. Full compliance with the defined limits is observed. The lack of particle size limits for the active substance has been justified by demonstrating that the formulation, not the particle size of the active substance is the limiting factor for dissolution. A copy of the specification of the dosage form manufacturer has been provided. The active substance is manufactured in accordance with the principles of good manufacturing practice for starting materials.

Other Substances

Calcium sulphate dihydrate and carmellose sodium comply with their requirements of the Ph. Eur. Copies of the Ph. Eur. monographs and a satisfactory example certificate of analysis for one batch of each have been presented.

Potable water is used during granulation. The specification includes the control of chemical and microbiological parameters. Appropriate justification for the use of potable water in the granulation of premixes has been provided.

Packaging Materials

The authorised pack comprises a double layer, low-density polyethylene bag available in capacities of 2, 3, 4.8, 6.4, 8, 9, 12, 16, 20 and 25 kg. The inner layer is opaque white with pharmaceutical quality UV shield and any printing is applied to the outer layer that also has an anti-slip coating. Specifications are presented for each pack size. The thickness of the polyethylene increases as the pack size increases (2, 3, 4 kg are 120μm; 9, 12 and 16 kg are 180 μm; 20 and 25 kg are ~ 200 μm). The applicant has provided an assurance that the polyethylene used is of food-contact quality. Cardboard cartons containing 8 x 3 kg polyethylene bags, 12 x 2 kg polyethylene bags are also available.

Manufacture of the Finished Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licenced manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines.

Finished Product Quality Control

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

Stability

Active substance

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Finished Product

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Stability studies were undertaken on three consecutive pilot scale (250 kg) batches of the final product manufactured in April 2003. Samples were stored in packs simulating the final marketing pack and kept under real time conditions (25°C/60 % RH) for up to 24 months, intermediate conditions (30°C/60 % RH) where required and accelerated conditions (40°C/75 % RH) for up to six months with one additional time point at 13.5 months also being examined. All results for the test parameters were within the proposed specification and the data supported the applicant's proposed shelf-life of 24 months with no specific storage conditions. Recent data provided under a variation procedure, from September 2014, enabled the finished product shelf-life to be raised to 36 months.

In-Use
For opened containers a shelf-life of two weeks has been justified. In support of this, one batch of the 10 % premix was stored in an opened pack at 25°C/60 % RH for 14 days. No significant change in appearance, moisture, pH, assay or 4-epi-CTC levels was observed.

Data were also provided for both pig and broiler feed in mash and pellet form. On the basis of these data, a 3 month shelf life after incorporation into feed was justified for both mash and pelleted feed.

CONCLUSIONS ON QUALITY
The product can be supported with respect to quality. Appropriate storage conditions have been stipulated to ensure the quality of the product is maintained throughout its shelf-life.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies
The applicant has provided reference to a comparison of dissolution of Aurofac 100 Granular versus Aurofac 250 Granular. The report concluded that there is equivalence between the dissolution profiles of the two products. The concentration of active substance in the gastro-intestinal tract where dissolution and absorption will take place will be the same for both test and reference products; therefore exemption 4c of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products applies.

Toxicological Studies
The toxicological aspects of this product are identical to the reference product Aurofac 100 Granular. Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to consumers and users.

User Safety
The currently authorised user safety warnings appear to be adequate to protect the end user, as well as those involved in milling the product into the feed. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity
The applicant refers to the previously submitted Environmental Risk Assessment for Aurofac 100 Granular. This also applies to Aurofac 250 Granular since the in-use concentration and posology is the same.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies
No residue depletion studies have been provided since a dissolution study has been provided which (as assessed in Part IV below) shows bioequivalence between this product and Aurofac 100 Granular.

Chlortetracycline hydrochloride is listed in Annex I of Council Regulation 2377/90 (O.J. 281/96). The marker residue is sum of parent drug and its 4-epimer.

MRLs are listed below:

	All food producing species.
Muscle	100 µg/kg
Liver	300 µg/kg
Kidney	600 µg/kg
Milk	100 µg/kg

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

Pigs: 10 days
Chickens (meat): 2 days
Turkeys (meat): 2 days
Ducks (meat): 4 days

Not authorised for use in laying birds producing eggs for human consumption.
Do not use within 14 days of the onset of laying.

The variation was approved in February 2011 to remove laying birds from the indication as a target species

IV. CLINICAL ASSESSMENT (EFFICACY)
IV.A Pre-Clinical Studies

Pharmacodynamics
As the applicant states, for a generic application, there is no requirement to present pharmacodynamic data.

Tetracyclines are broad spectrum antibiotics with activity against gram-positive and gram-negative bacteria, including some anaerobes. They are also active against chlamydia, mycoplasma, rickettsia and some protozoa. Tetracyclines act by inhibiting protein synthesis, binding reversibly to receptors of the 30S ribosomal subunit of susceptible microbes. Initial binding blocks the later binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosomal complex, preventing the addition of new amino acids to new peptide chains, inhibiting protein synthesis.

The information provided in Section 5.1 of the SPC is considered accurate and satisfactory for this type of application.

Pharmacodynamics

There is no difference in the actual constituents of both formulations, and the products are mixed into feed to achieve the same in feed inclusion rate. Differences are limited to differences in the proportions of the relative contents of the formulations. Therefore there is no requirement to submit an *in vivo* bioequivalence study and the applicant has submitted an *in vitro* study comparing the dissolution profiles of Aurofac 250 Granular and Aurofac 100 Granular. The dissolution studies submitted were appropriate to demonstrate bioequivalence between Aurofac 100 Granular and Aurofac 250 Granular.

Tolerance in the Target Species of Animals

As the dissolution rates are similar, the products can be considered bioequivalent, therefore no new target species tolerance data have been presented. The information provided is considered satisfactory for this type of application. The information given in the SPC is also considered suitable.

Resistance

Since the in-feed concentration of Aurofac 250 Granular is to remain the same as that for Aurofac 100 Granular, and the use of the products will be substitutive rather than additive, the risk of induction of resistance will be no greater than from Aurofac 100 Granular. This application is based on essential similarity with bioequivalence to Aurofac 100 Granular; therefore no new data are required with regard to demonstration of resistance potential for Aurofac.

IV.B Clinical Studies

No new studies on efficacy have been presented because of the nature of the application. The same basic claims and warnings can be permitted for Aurofac 250 Granular as those authorised for Aurofac 100 Granular.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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.

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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.

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