



# PorkFACTS™

## AN UPDATE OF RECENT SWINE RESEARCH

### Aureomycin® vs Generics: Comparative Release of Chlortetracycline from Premix Formulations

#### ► SUMMARY

Two studies investigated drug release characteristics of different brands of granular chlortetracycline (CTC) premixes. Feeds fortified with Aureomycin® premixes released, on average, 37% more CTC into simulated gastric fluids compared to generic premixes. Aureomycin premixes also significantly improved the uniformity of *in vivo* drug exposure to CTC (time exceeding plasma levels of 0.5 µg/mL), thereby enhancing the predictability of therapeutic outcomes. An odds ratio analysis by Dr. John Deen, University of Minnesota, showed that pigs fed Aureomycin 90G were 9% more likely than Pennchlor 100G to achieve therapeutic blood and lung levels; pigs fed Aureomycin 220G were 13% more likely than Chlor 100 to achieve therapeutic blood and lung levels.

**Aureomycin  
premixes release  
more CTC into  
gastric fluids than  
generic premixes,  
and maintain more  
uniform plasma  
drug levels.**

#### ► RATIONALE

- The ultimate quality of an antimicrobial premix depends on the release of active ingredient *in vivo*. The drug must dissolve in gastrointestinal fluids before being absorbed by the enterocytes. Drug extraction, therefore, is critical for the success of a dosing regimen because it determines how much antibiotic will become available to reach the site of infection.
- The pharmacokinetic properties of chlortetracycline (CTC) in swine allow drug administration via the feed to achieve therapeutic concentrations *in vivo* because the agent is readily absorbed from the intestinal lumen.<sup>1</sup>
- Factors hindering the dissolution of feed-administered CTC in swine may be associated with formulation differences among premixes.<sup>2</sup> Three types of factors affecting release of active ingredient in the premix include: 1) the choice of excipient (i.e., carriers, diluters, stabilizers, etc.); 2) the granulation process that makes granules to possess some porosity (i.e., pore size and number of pores) and granule hardness (the harder the granule the more difficult it is to dissolve); 3) the particle size that governs the surface area exposed to digestive juices (the smaller the granule, the larger the relative surface area).
- Tetracyclines complex with multivalent cations used as carriers in the premix, and at intestinal pH these chelates precipitate and become unavailable to intestinal absorption.<sup>3</sup> Because the types and proportions of excipients differ across premixes,<sup>1</sup> the rates and extents of CTC release may vary substantially from one premix to another, and may affect the accumulation of CTC in tissues.

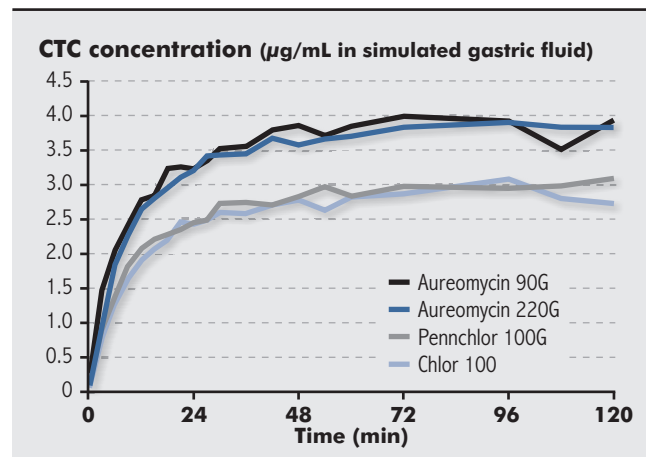
## ▶ EXPERIMENT DESIGN

- Two studies were designed to compare the ability of different brands of granular CTC premixes to release their content of drug in simulated gastrointestinal fluids, and to assess plasma accumulation of CTC in pigs fed rations fortified with the test premixes.<sup>4</sup>
- The studies evaluated 4 brands of granular CTC premix available in North America: Aureomycin 90G (US; Alpharma Animal Health) and Aureomycin 220G (Canada; Alpharma Animal Health; equivalent to Aureomycin 100G marketed in the US), Chlor 100 (Canada; Bio-Agri-Mix Ltd), and Pennchlor® 100G (US; Pennfield Oil Co.). The label potency of Aureomycin 90G is 90 g CTC/lb product (198 g/kg), and that of the other premixes is 100 g CTC/lb product (220 g/kg). All tests were conducted under randomized, double-blind conditions.
- Experiment 1 (*in vitro* dissolution study): The USP standard dissolution testing method<sup>5</sup> was used to document the drug dissolution profile of the medicated feeds. The time-course of CTC dissolution in simulated gastric fluid (400 mL, pH 1.6, 40°C for 2 h) was subject to mathematical modeling that described the dissolution of CTC and interactions (e.g., sorption and desorption) of dissolved CTC with feed components.
- Experiment 2 (*in vivo* steady-state accumulation study): Sixteen castrated male pigs (10 kg) were used in 4 replicates of a parallel experiment where all premixes were tested once per replicate. After a 7-day acclimation period, pigs were individually fed rations fortified with 550 ppm CTC at 12-h intervals in quantities corresponding to 2% of body weight. Blood samples were obtained over time following the 1st, 7th (at steady state), and 9th consecutive medicated meal, and CTC concentrations assessed.
- A plasma concentration of 0.5 µg/mL was deemed the target drug level that must be reached for 100% of the dosing interval (this target was derived by considering the time-dependent antibacterial activity of the tetracyclines,<sup>6</sup> the MIC distributions of PRDC pathogens for which CTC is prescribed,<sup>7</sup> and the results of previous pharmacokinetic/pharmacodynamic studies with an *Actinobacillus pleuropneumoniae* infection model<sup>8,9</sup>). Plasma CTC accumulation is indicative of lung accumulation because the drug readily equilibrates between plasma and lung tissue; CTC lung tissue levels could be expected to be up to 3-times higher than plasma levels.<sup>10</sup>

**The brand of premix was the greatest determinant of CTC release in simulated gastric fluids.**

## ▶ RESULTS EXPERIMENT 1

- Figure 1 summarizes the average concentration of dissolved CTC released into the simulated gastric fluids as a function of time. The type/brand of premix was the greatest determinant of CTC release. At the linear phase of CTC release, the rate of increase in drug concentration was significantly greater ( $P=0.0186$ ) for the Aureomycin-medicated feeds than for the feeds containing Chlor 100 and Pennchlor 100G.



**FIGURE 1:** Average time-course of CTC concentrations in simulated gastric fluid (concentrations normalized for a 176 ppm in-feed CTC concentration).

**Aureomycin generated the most uniform duration of CTC plasma drug exposure.**

- Figure 2 presents the relative percent of CTC released in simulated gastric fluid from medicated feed. This estimator of efficiency in drug release was significantly different across CTC premixes ( $P=0.0269$ ). Feeds containing Aureomycin released, on average, 37% more CTC than feeds containing Chlor 100 or Pennchlor 100G.
- These results support the hypothesis that the rate and extent of CTC release from medicated feed is significantly impacted by brand of premix.

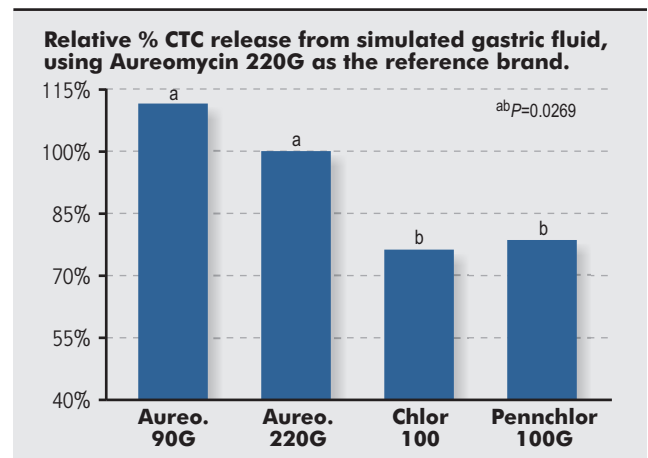
## RESULTS EXPERIMENT 2

**Feed intake was deterred in some pigs by the inferior palatability of the generic premixes.**

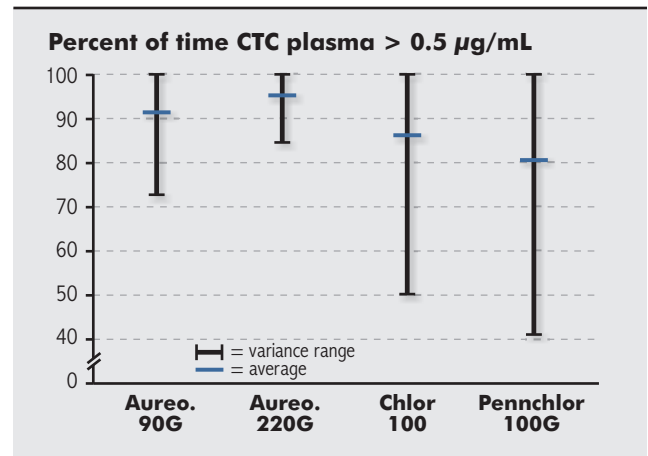
- Plasma pharmacokinetic profiles were similar among pigs fed diets fortified with Aureomycin 220G, but the other CTC-medicated feeds showed greater variation in plasma profiles among pigs, especially in the Chlor 100 and the Pennchlor 100G groups. Pigs fed Aureomycin 220G had slightly higher plasma concentrations at steady state than those of the other treatment groups, especially at the time of euthanasia.
- Figure 3 shows that variation in the duration of exposure to plasma CTC concentrations above the target concentration ( $0.5 \mu\text{g/mL}$ ) differed among treatment groups. Aureomycin 220G provided the most uniform CTC plasma exposure, but Aureomycin 90G was statistically similar ( $P=0.2014$ ). In contrast, significantly greater variances in plasma exposure to CTC were detected with Chlor 100 ( $P=0.0242$ ) and Pennchlor 100G ( $P=0.0408$ ).

**Pigs fed Chlor 100 and Pennchlor 100G had up to 14 hours/day of sub-therapeutic CTC exposure.**

- Pigs in the Chlor 100 and Pennchlor 100G treatment groups experienced as much as 14 hours/day of steady-state exposure to sub-therapeutic CTC concentrations, a situation that can increase selection pressures for drug-resistant bacteria during therapy, and contribute to disease relapse after cessation of the dosing regimen. Thus, the therapeutic efficacy of dosing regimens using these CTC premixes is very difficult to predict in a context of herd therapeutics.
- Reduced feed intake was also observed in some pigs offered rations medicated with Chlor 100 and Pennchlor 100G, apparently due to inferior palatability. This consequence may further erode *in vivo* drug concentrations available to inhibit susceptible pathogens.



**FIGURE 2:** Proportion of feed-administered CTC that dissolved in simulated gastric fluid.



**FIGURE 3:** Variation in the duration of therapeutic CTC plasma concentrations in pigs given feeds fortified with 4 premix brands.

## ▶ CONCLUSIONS

**Drug release characteristics of Aureomycin contribute to favorable therapeutic outcomes.**

**Pigs fed Aureomycin were 9-13% more likely to achieve therapeutic blood and lung levels.**

- Feed has a marked effect on the release and dissolution of CTC from feed-grade premixes. The extent of this effect depends on the type of premix used in the preparation of the medicated feed. Aureomycin premixes released, on average, 37% more CTC than the generic premixes.
- Plasma therapeutic concentrations were maintained more consistently in pigs given Aureomycin-medicated feeds. In addition, plasma CTC levels are predictive of CTC lung tissue levels, which can be expected to be up to 3-times higher than plasma concentrations.
- An odds ratio analysis by Dr. John Deen, University of Minnesota, showed that pigs fed Aureomycin 90G were 9% more likely than Pennchlor 100G to achieve therapeutic blood and lung levels; pigs fed Aureomycin 220G were 13% more likely than Chlor 100 to achieve therapeutic blood and lung levels.
- Aureomycin 220G produced the most uniform exposure to CTC in pigs, which improves the predictability of therapeutic outcome. Aureomycin 90G produced a slightly less uniform exposure but was not significantly different from Aureomycin 220G. In contrast, CTC exposure with Chlor 100 and Pennchlor 100G was significantly more variable than with Aureomycin 220G.
- Chlor 100 and Pennchlor 100G had a deterrent effect on the initial feed consumption of a number of pigs, a situation that may further compromise the efficacy of therapeutic feed-grade regimens employing these products.
- It is noteworthy that all the tested premixes are deemed “bioequivalent” by regulatory agencies, but study results question the therapeutic equivalence of these premixes.
- Desirable milling characteristics of feed-grade premixes (e.g., granulation) must not compromise their ability to release their antibiotic content and fight infection. Results from these studies suggest that release characteristics are compromised in the manufacture of some CTC granular premixes.

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