KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
www.KeepAntibioticsWorking.org

May 12, 2021

Dr. Janet Woodcock
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Acting Commissioner Woodcock,

Keep Antibiotics Working (KAW)[1] is writing to inform you of a marketing campaign by Zoetis that promotes the feeding of chlortetracycline (CTC) at a treatment dose for longer than the 5 days allowed by the approved label. In addition, Zoetis' campaign promotes the use of chlortetracycline for disease control at a dose that is only allowed for disease treatment. Both the extra-label duration and the extra-label indication are prohibited under federal law. We ask that you investigate this and act against this specific promotional campaign. Further we ask that you clarify to drug makers, drug users, and veterinarians that these types of extra-label uses are prohibited for drugs used in animal feeds. The unethical behavior by Zoetis, the world's largest animal drug maker, brings into question the animal drug industry's commitment to antimicrobial stewardship.

On their website, across multiple webpages Zoetis recommends pulse feeding CTC.[2] Pulse feeding refers to feeding CTC at a treatment dose for the 5 days allowed by the label, withdrawing the drug for two days, and then administering the drug for another 5 day "pulse." Additional pulses can be added. Aureomycin at 10 mg CTC/lb is approved for use in beef cattle for the treatment of bacterial enteritis and pneumonia and the label clearly states "feed for not more than five days". Thus, when a veterinarian recommends repeat pulsing it is an extra-label use, which is prohibited under federal regulations for medicated animal feeds.[3] A veterinarian could write an additional veterinarian's order after a five-day treatment if there was no improvement in the animal being treated. However, this is not the same as recommending multiple pulses of 5-day treatments with 48 hours in between administration.[4] Despite this, repeat pulsing is openly promoted by Zoetis. On their website Tom Peters, PhD, ruminant nutritionist, is quoted saying, "In our covered feeding systems, I work with the consulting veterinarians to pulse with AUREOMYCIN in our starter programs on ***almost all*** of our cattle." The website also states that *many* feedlot operators are finding success with the pulsing approach for treatment of BRD.

[1] Keep Antibiotics Working is a coalition of 20 public health, consumer, animal protection and other non-profit organizations, that has advocated for smarter usage on farms of the antibiotics most precious to people.
[2] Zoetis. "Chlortetracycline Pulses Cost-Effective Treatment for BRD." BRD Solutions from Zoetis. Accessed May 4, 2021. https://www.brd-solutions.com/insights/chlortetracycline-pulses-cost-effective-treatment-for-brd.aspx.;
Zoetis. "The Value of In-Feed Chlortetracycline in Starting Cattle." zoetisus.com. Revised May, 2016. Accessed May 4, 2021. https://www.zoetisus.com/products/beef/feed-additive-solutions/docs/value-of-in-feeed-chlortetracycline.pdf ;
Zoetis. "Cattle Feed Additive Treatments." zoetisus.com. Accessed May 12, 2021. https://www.zoetisus.com/products/beef/feed-additive-solutions/treatments.aspx#.
[3] 21 CFR 530.11
[4] Dewell, Grant and Loy, Dan. "Feeding CTC to Feedlot Cattle." *Iowa State University Extension and Outreach*, March 2017, 2. https://vetmed.iastate.edu/sites/default/files/VDPAM/Extension/Beef/2017%20CTC%20feedlot%20cattle.pdf.

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Zoetis also suggests using "DRAXXIN® (tulathromycin) injectable solution on arrival, followed by three five-day pulses of AUREOMYCIN as recommended by the attending veterinarian (Days 6-10, 12-16 and 18-22)" in high risk cattle. The metaphylactic injection of a critically important macrolide (tulathromycin) followed by pulses of tetracycline creates serious antibiotic resistance concerns. Researchers Kanwar et al. have demonstrated that pulsing CTC after treating steers with the third-generation cephalosporin ceftiofur exacerbates ceftiofur resistance and should be avoided. Similar resistance mechanisms may exist for macrolides and CTC.[5]

The recommendation to use pulses of CTC after metaphylactic tulathromycin violates FDA rules by promoting an extra-label indication. The tulathromycin study included on the web page describes *control* of bovine respiratory disease, while the label only allows the drug to be used at 10 mg CTC/lb for *treatment*. Zoetis blurs the distinction between treatment and control in their promotional materials by labeling the page "BRD [Bovine Respiratory Disease] Treatment" but then referencing their study that uses pulses of chlortetracycline after metaphylactic use in "high risk animals". Metaphylaxis refers to disease control not treatment. Similarly, treatment does not describe use in "high risk animals" but instead refers to administering antibiotics to animals that are clinically ill.

Considering the influence Zoetis has as the world's largest animal health company, this marketing campaign is completely irresponsible and detrimental to national antibiotic stewardship and public health. Sales of medically important tetracyclines, which have represented the largest volume of domestic sales for use in animals since data have been reported, jumped an additional 4% this last year.[6] The promotion and practice of pulse feeding throughout the cattle industry may be significantly contributing to the high level of sales and the recent rise.

The use of antibiotics for long periods of time increases the risk of antibiotic resistance. Because of this, FDA is currently accepting comments on how to set limited durations for antibiotics in animal feeds that do not have them.[7] If drug makers can promote ignoring these limits as Zoetis does in this marketing campaign and veterinarians can write orders that ignore them, then the effort to set durations limits will be completely ineffective at addressing resistance.

KAW has repeatedly requested the FDA do more to address unethical marketing of medically important drugs. We urge FDA to act on illegal advertising including this marketing campaign by Zoetis and thoroughly educate producers and veterinarians on the restrictions on extra-label use. FDA should clarify that duration limits are actual limits to be followed. Failure to address unethical marketing of antibiotics by drug makers completely undermines the efforts of FDA to promote antibiotic stewardship and puts public health at risk.

Sincerely,

Steven Roach, Food Safety Program Manager, Food Animal Concerns Trust
on behalf of Keep Antibiotics Working member organizations

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[5] Kanwar, Neena, et al. "Effects of Ceftiofur and Chlortetracycline Treatment Strategies on Antimicrobial Susceptibility and on Tet(A), Tet(B), and Bla CMY-2 Resistance Genes among E. Coli Isolated from the Feces of Feedlot Cattle." *PLoS ONE* 8, no. 11 (November 19, 2013). https://doi.org/10.1371/journal.pone.0080575.

[6] US Food and Drug Administration. "2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals". December 2020. https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2019-use-food-producing.

[7] US Food and Drug Administration. "FDA Seeks Public Comment on Potential Approach for Defining Durations of Use for Certain Medically Important Antimicrobial Drugs for Food Animals." February 2021. www.fda.gov/animal-veterinary/cvm-updates/fda-seeks-public-comment-potential-approach-defining-durations-use-certain-medically-important.