December 4, 2012

The Honorable Margaret Hamburg, Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

Dear Commissioner Hamburg:

We are writing to inform you of the results of new tests of pathogens and of ractopamine levels in pork products appearing in the January, 2013 issue of Consumer Reports, to urge the U.S. Food and Drug Administration (FDA) to prohibit the use of antibiotics in livestock except for treatment of disease, and to revoke approval for use of ractopamine in pork.

I. Ractopamine

Consumer Reports tested some 240 pork products for ractopamine, a drug used in pork, beef, and turkey production to promote weight gain and enhance feed efficiency. Very low, but detectable, levels of ractopamine between 1 and 5 parts per billion (ppb) were found in about one-fifth of the samples tested for the drug. Although the ractopamine levels in the samples we tested were significantly below FDA’s Maximum Residue Level (MRL) of 50 parts per billion (ppb), we strongly disagree with the safety assessment that led to this MRL and agree with the European Union (EU) that no MRL can be set for ractopamine given the present data.

As you know, in December 1999, FDA approved ractopamine hydrochloride (Paylean, NADA 140-863) for use in finishing pigs. In 2012, using a six volunteer human study, the Codex Alimentarius Commission voted to adopt a much lower MRL of 10 ppb. The EU and China, however, both considered the available studies inadequate to set an MRL and so prohibit the use of ractopamine.
We believe the FDA MRL should be reconsidered. We do not think ractopamine meets the FDA safety standard of “safe and effective for a specific use in a specific animal species … [and] that food made from animals treated with the drug is safe for people to eat.”1 FDA based their MRL for ractopamine on a study done in rhesus monkeys, in which the agency determined it showed a no-observed-effect level (NOEL) of 125 μg/kg-bw.2 In choosing the NOEL from the rhesus monkey study, we believe that FDA ignored important data for setting safety limits from a dog study and a human study in the same NADA (e.g. NADA 140-863). The dog study determined a NOEL of 2 μg/kg-bw, while the human study had a NOEL of 99 μg/kg-bw.3 Further, the NOEL for humans, i.e., 99 μg/kg-bw, was based on an overall/composite value for the three cardiac function variables tested, not the NOEL for the most sensitive variable, the cardiac output, for which the NOEL was 83 μg/kg-bw. We strongly believe that using an average or composite value for a NOEL, rather than the lowest NOEL, contradicts the meaning/purpose of a NOEL, thereby making it not be a true NOEL. In other words, the NOEL for rhesus monkeys was more than 60-times higher than the value for dogs, and some 50 percent higher than the most sensitive NOEL for humans. Thus, we do not think that FDA used the most sensitive species (dog) when developing their MRL for ractopamine in pig tissue. We are aware that FDA’s rationale for not using the most sensitive species, e.g. dog, was that the rhesus monkey 24-hour clearance rate for an oral dose of ractopamine via urine was closer to that of humans compared to dogs, e.g. 42% and 45% versus 54%, respectively, and that FDA “concluded that the primate model is more predictive of the human acute toxicity response to oral exposure to RACT [ractopamine] than the canine model.”4 However, we believe that the difference in clearance rates is small and does not justify a failure to base the standard on the most sensitive species, i.e. dogs. We also question why FDA had human data, yet chose to base its standard on monkey data for which there was a higher NOEL than provided by the human data.

In addition, the European Food Safety Authority (EFSA) performed a more in-depth analysis of the human study on ractopamine referenced in NADA 140-863. As you are aware, ractopamine was originally developed as a treatment for asthma, although it was never approved for that use, and a study was conducted to assess the dose-effect response in humans. The study involved six healthy adult men who were given single oral doses of ractopamine from 5 mg through 40 mg and followed for 24 hours. As EFSA noted, in three out of the six men, there were effects seen in several parameters related to cardiac health at the lowest dose tested, 5 mg.5 Furthermore, population subsets which may be more sensitive to β-andrenergic drugs—such as people with cardiac disease (15% of the population), children, or individuals with specific β-receptor polymorphism—were not adequately considered. This information, along with the small sample size, caused EFSA to conclude that a NOEL could not be set, based on the human data. Consequently, EFSA felt that neither an acceptable daily intake (ADI) nor an MRL could be

1 See: http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/UnapprovedAnimalDrugs/ucm229084.htm
3 IBID
4 Pg. 41 in IBID.
established. We agree. We disagree with FDA that the submitted safety data allow them to set a “safe” level for ractopamine in pig meat, i.e., set a level that meets the legal criterion “that food made from animals treated with the drug is safe for people to eat.”

We are also concerned about the unexpected adverse drug event (ADE) reports associated with ractopamine. In September 2002, FDA sent a warning letter to Elanco Animal Health for failing to report ADEs, including 22 reports of stress, stiffness, deaths and other effect of pigs. We note that in a March 2011 summary of Cumulative Veterinary Adverse Drug Experience (ADE) Reports, there were some 218,116 pigs that had been fed Paylean (ractopamine) and for whom an adverse event was reported, with the top ten most frequently reported signs being “death, recumbency, lameness, hyperactivity, reluctant to move, stiffness, trembling, dyspnea, collapse, and hoof disorder”. (In March, 2012, FDA stated to media that they had looked at the ADE reports for ractopamine and, after excluding reports of ineffectiveness, meat abnormalities and fertility abnormalities, the number of animals with ADE reports associated with ractopamine was reduced to 160,917.) Furthermore, scientific studies have shown the ractopamine increases aggressive behavior, especially in gilts. The large number of ADE reports associated with ractopamine use in pigs, along with the studies showing it increases aggressive behavior, demonstrates that this drug is not safe for pigs. Thus, we feel ractopamine does not meet the criteria of being safe for animals.

In summary, given the above data on human and animal safety, we do not think ractopamine meets FDA safety standards of “safe and effective for a specific use in a specific animal species” nor “that food made from animals treated with the drug is safe for people to eat.” Thus, we strongly urge FDA to pull ractopamine from the market.

---

6 FDA’s Concerns about Unapproved Animal Drugs. At: http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/UnapprovedAnimalDrugs/ucm229084.htm
8 click on N-S – ADE Summaries and see page 179 in: http://web.archive.org/web/20110411125255/http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055394.htm
11 See: http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/UnapprovedAnimalDrugs/ucm229084.htm
II. Antimicrobial Resistance

*Consumer Reports* tested some 198 pork chop and ground-pork samples, purchased at retail from six U.S. cities, for four pathogens: *Staphylococcus aureus, Salmonella, Listeria monocytogenes*, and *Y. enterocolitica* and for one indicator organism, *Enterococcus*. Although our testing found *Salmonella, Staphylococcus aureus* and *Listeria monocytogenes* in only 3 to 7 percent of the samples, more than two-thirds of these samples, i.e. some 69%, tested positive for *Y. enterocolitica*.12

We also found high levels of antimicrobial resistance in the various pathogens and indicator organisms. For example, 121 of the 132 samples, or more than 90 percent, that tested positive for *Y. enterocolitica* were also resistant to one or more antibiotics, with over 39 percent (52 of 132) being resistant to two or more antibiotics. Thirteen of 14 (or 93%) *Staphylococcus aureus* samples were resistant to one or more antibiotics, as were six of eight (or 66.6%) *Salmonella* samples, and 12 of 19 (or 63%) *Enterococcus* samples. The high level of resistance to antibiotics that we found in the pathogens and indicator organism is of great concern to us. Thus, we urge FDA to ban all uses of antimicrobial products in animal agriculture, except for treatment of veterinarian-identified sick animals.

Thank you for your prompt consideration of these concerns. Please let us know how we may assist you in your efforts to address these critical matters.

Sincerely,

Michael Hansen, PhD
Senior Scientist

Urvashi Rangan, PhD
Director of Consumer Safety and Sustainability

Cc: Michael Taylor, Deputy Commissioner for Foods

---