April 2, 2009
Dr. Joshua M. Sharfstein, Deputy Commissioner
United States Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Deputy Commissioner Sharfstein,

We are writing on behalf of the Alliance for the Prudent Use of Antibiotics (APUA), a science-based public health organization established in 1981 to preserve the power of antibiotics. We have followed your agency's work related to antibiotic resistance over the years. We have been pleased with several public health protections instituted including the veterinary drug risk analysis, the 2005 decision to remove fluoroquinolone use from poultry production, and the NARMS surveillance program.

While these protections move in the right direction, they do not match the degree of the increasing concern in clinical circles about the drug resistance threats that we face. We are especially concerned that the agency is lagging in its responsibilities to halt the unwarranted use of critically important human antibiotics in farm animals. Likewise, deferred releases of risk assessments for penicillin and other veterinary drug reviews may cause inconsistent delays in public health protection measures.

In the last few years, the US Dept of Homeland Security and the CIA have joined the IDSA, WHO and CDC, ASM, and other clinical groups in highlighting antibiotic resistance as a national security threat. A Homeland Security-sponsored panel, which met at APUA last June, provided new evidence that the farm is a prodigious source of resistant bacteria that transfer directly from food and spread in the waterways and soil to evolve into more dangerous multi-resistant bacteria that can infect humans. (See attached AMROAR Scientific Meeting Report).

The indiscriminate use of broad-spectrum antibiotics in agriculture important to human medicine is of particular concern in light of alarming increases in untreatable gram-negative infections in the US. In addition, occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections has grown from only two percent of the total number of staph infections in 1974 to 63% in 2004. At the same time, novel and affordable antibiotics are not being developed to replace the antibiotics that are losing their power. Any incidence of disease that does not respond to current therapies may result in an epidemic of untreatable infections.

Based on these concerns, we reiterate our support of the 2006 recommendation by the Veterinary Medicine Advisory Committee to not approve the use of cefquinome, a fourth-generation cephalosporin antibiotic, for use in agriculture. Cefquinome exposure can result in resistance to other cephalosporin antibiotics, including the medically important cefepime, one of the few remaining treatment options for infections caused by extended spectrum beta-lactamases, including CTX-M-15. These are produced by certain commensal and pathogenic bacteria,

75 Kneeland Street, Boston MA, 02115
Phone: 617.636.0966 Fax: 617.636.3999 www.apua.org

including *Escherichia coli*, and can cause infections directly, or serve as a reservoir of resistance genes, which can then be transferred to other bacterial species. In Europe, where cefquinome has been approved for use in livestock since 1994, CTX-M beta lactamases account for a large fraction of ESBLs, and the majority of these infections are community-acquired.

For similar reasons, we recommend that FDA reissue the ban on extra-label use of cephalosporins in agriculture. In July of 2008, FDA determined that the extra-label use of cephalosporins in food-producing animals presents a risk to human health and should be prohibited. A study by the Canadian Integrated Program for Antimicrobial Resistance Surveillance found that "off-label" use of ceftiofur, a 3rd generation cephalosporin, was associated with increasing numbers of cephalosporin resistant salmonella in both animals and humans in Quebec. This resulted in a voluntary withdrawal in chicken hatcheries of extra-label use of ceftiofur. A significant decrease in ceftiofur-resistance was seen in *Salmonella Heidelberg* isolates from chickens and humans following the withdrawal. However, in November of 2008, the FDA rescinded the order, again allowing the build-up of antibiotic resistant genes on the farm and related environments, which will lead to more resistant infections in humans throughout the country.

The time is overdue for the CVM to formalize a more public health-oriented framework for veterinary drug approvals, reflecting the best scientific evidence that takes into account increasing human health concerns. The 2002 APUA FAAIR Report, (Clinical Infectious Diseases, Volume 34) provides the scientific consensus, and suggests specific policy recommendations with regard to agricultural use of antibiotics:

- Antimicrobial agents should not be used in agriculture in the absence of disease
    - Use of antimicrobials for economic purposes such as growth promotion or feed efficiency should be discontinued
    - Because of their critical role in treating human disease, 3rd generation or higher cephalosporins should not be used in agriculture except to treat indicated infections in individual animals.
- Antimicrobials should be administered to animals only when prescribed by a veterinarian
- Quantitative data on antimicrobial use in agriculture should be made available to inform public policy
- The ecology of antimicrobial resistance in the environment should be considered in assessing human health risk associated with antimicrobial use in agriculture
- Surveillance programs for antimicrobial resistance should be improved and expanded
- The ecology of antimicrobial resistance in agriculture should be a research priority

We support increased funding for the work of the agency to control drug resistance, and remain available to assist with any scientific and clinical guidance. We support the principles of the Keep Antibiotics Working Group and its endeavors to contain the growing crisis of antimicrobial resistance. We thank you for your consideration.

Sincerely,

Stuart B. Levy, MD, President, APUA

Kathleen T. Young, Executive Director, APUA

Attachment: AMROAR Scientific Meeting Report 2008

75 Kneeland Street, Boston MA, 02115
Phone: 617.636.0966 Fax: 617.636.3999 www.apua.org