

Preserving the Power of Antibiotics®



APUA

ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS

Chief Executive Officers

Stuart B. Levy, President
Thomas F. O'Brien, Vice President
Kathleen T. Young, Executive Director

Board of Directors

Stuart B. Levy, Chairperson
Harris A. Berman
Gordon W. Grundy
Bonnie Marshall
Thomas F. O'Brien
Arnold G. Reinhold
Stephen C. Schoenbaum
Philip D. Watson

Scientific Advisory Board

Jacques F. Acar, France
Werner Arber, Switzerland
Fernando Baquero, Spain
Michael L. Bennis, USA
Patrice Courvalin, France
Otto Cars, Sweden
Jose Ramiro Cruz, Guatemala
Iwan Darmansjah, Indonesia
Julian Davies, Canada
Paul Farmer, Haiti
Walter Gilbert, USA
Herman Goossens, Belgium
Sherwood L. Gorbach, USA
Ian M. Gould, Scotland
George Jacoby, USA
Sam Kariuki, Kenya
Ellen L. Koenig, Dominican Republic
Calvin M. Kunin, USA
Jacobo Kupersztoch, USA
Joshua Lederberg, USA
Stephen A. Lerner, USA
Jay A. Levy, USA
Donald E. Low, Canada
Scott McEwen, Canada
Jos. W.M. van der Meer, The Netherlands
Richard P. Novick, USA
Iruka Okeke, USA & Nigeria
Maria Eugenia Pinto, Chile
Vidal Rodriguez-Lemoine, Venezuela
José Ignacio Santos, Mexico
Mervyn Shapiro, Israel
K. B. Sharma, India
Atef M. Shibl, Saudi Arabia
E. John Threlfall, United Kingdom
Alexander Tomasz, USA
Thelma E. Tupasi, Philippines
Anne K. Vidaver, USA
Fu Wang, China
Thomas E. Wellems, USA
Bernd Wiedemann, Germany

Headquarters

APUA
75 Kneeland Street
Boston, MA 02111
USA

Telephone: 617-636-0966
Fax: 617-636-3999
Email: APUA@tufts.edu
Website: www.APUA.org

December 1, 2006

Andrew C. von Eschenbach, M.D.
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane,
Rockville MD 20857-000

Dear Acting Commissioner von Eschenbach,

We are writing to support the recommendation of the VMAC to reject and not approve the use of cefquinome, a fourth-generation cephalosporin antibiotic, for use in animal agriculture. One area that is critical in assessing the potential effects of cefquinome use is the exposure of non-target organisms, including opportunistic pathogens such as *Escherichia coli*.

Cefquinome exposure can result in resistance to other cephalosporin antibiotics, including the medically-important antibiotic cefepime. Decreased cefepime sensitivity and resistance is due, in large part, to extended-spectrum beta-lactamases (ESBLs), including CTM-X-15. These genetically mobile genes have been observed at clinically significant frequencies in many countries, and are increasing in frequency in the U.S. Cefquinome use in agriculture, especially with no specific limitations on off-label use, will increase the prevalence of these powerful antibiotic resistance genes.

Since many disease-causing bacteria are both pathogens as well as components of the normal microbiota in animals and people (e.g., *E. coli*), cefquinome use will accelerate the replacement of older, less effective beta-lactamases with newer beta-lactamases that confer resistance to cefepime. These resistant bacteria then can either cause infections directly or serve as a reservoir of resistance genes which can then be transferred into other bacterial species. Evidence outside of the U.S. strongly indicates that this has already happened. For example, CTM-X-15 ESBLs have been isolated from *Salmonella* in Ireland and *E. coli* in Mexico. In Australia, resistance to older cephalosporins has occurred by a two-step process. First, an ESBL is acquired through gene transfer, and then followed by a very simple change in the bacterium's ability to take up the antibiotic. There is no reason to think this will not occur with cefquinome (and thus cefepime). The history of antibiotic resistance, in fact, suggests that if cefquinome is approved, cefquinome resistance will evolve. It would fly in the face of over a half-century's worth of scientific observation to conclude otherwise.

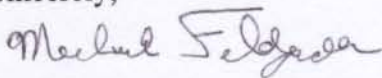
75 Kneeland Street • Boston, MA 02111-1901

Telephone: 617-636-0966 • Fax: 617-636-3999 • apua@tufts.edu • www.APUA.org

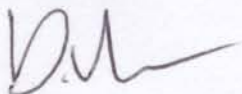
Another disturbing trend associated with cefepime resistance in non-target organisms is the correlation between cefepime resistance and resistance to other antibiotics. Resistance to cefepime in conjunction with resistance to other antibiotics can also lead to increased treatment failure, since many cefepime-resistant organisms are multidrug resistant. Consequently, we think it is premature to conclude that there will always be other options for treatment. Cefquinome/cefepime resistance will require that antibiotics of last resort be used for treatment of human infections. This will have tragic consequences for the mortality and morbidity associated with these infections, and it will also increase the economic burden of treatment.

Now is the time to take action *before* these ESBLs become established in similar bacterial populations in the U.S., not when it is already too late, particularly in light of the slowing discovery of novel antibiotics for human therapeutic use. We strongly urge you to follow the recommendation of the expert advisory panel and not release cefquinome for agricultural use, so that we may preserve the power of these life-saving drugs.

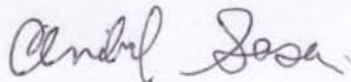
Sincerely,



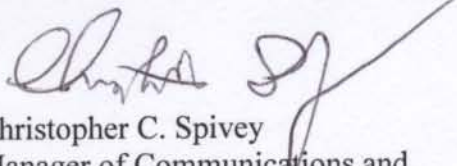
Michael Feldgarden, Ph.D.
Research Director, APUA



Susan Foster, Ph.D.
Director, Public Policy and Education, APUA



Anibal Sosa, MD
Director, International Program & Clinical Advisor, APUA



Christopher C. Spivey
Manager of Communications and
Business Development, APUA

cc:

Stephen F. Sundlof, D.V.M., Ph.D.