Food and Drug Administration, Department of Health and Human Services
Antimicrobial Resistance; Public Hearing [Docket No. FDA–2008–N–0225]; to be read by panel: 4/28/2008

Testimony:	Alliance for the Prudent Use of Antibiotics (APUA)
	75 Kneeland Street, Boston, MA 02111 (617-636-0966)
Drafted By:	Kathleen T. Young, Executive Director; Stuart B. Levy, MD, President
Cc:	Keely Macmillan

---

1) General information about the problem of antimicrobial resistance: Since the antibiotic era began, there have been three time periods when bacteria resistant to all existing antibiotics emerged and spread widely until a new antibiotic restored control. In the 1950s, strains of *Staphylococcus aureus* resistant to all available antibiotics (tetracycline, chloramphenicol, etc) raged throughout the world's hospitals until semi-synthetic penicillins and first-generation cephalosporins became available in the 1960s. Almost complete control was restored by the introduction of gentamicin and other newer aminoglycosides in the early 1970s, but then lost again in the late 1970s as plasmids encoding aminoglycoside-inactivating enzymes spread widely. The introduction in the early 1980s of three new classes of agents, third- generation cephalosporins, fluoroquinolones and carbapenems, each initially effective against nearly all gram-negative bacilli, began an unprecedented quarter century in which one or more agents has been available to treat almost any bacterial infection. In 2008 we have now reached another crisis of untreatable deadly infections. This time is dangerously different because the antibiotic pipeline is nearly empty. Many companies are leaving the antibiotic field to pursue more profitable investment for chronic illnesses and lifestyle disorders. In addition to posing a threat to the US healthcare system and our reliance on high tech medicine, resistant bacteria also represent a potential resource for adversaries to exploit in building biological weapons.

2) Containing antimicrobial resistance:

a) Antibiotics as a separate regulatory class: Because antibiotic misuse in one patient has such a broad impact on entire facilities and communities, APUA advocates that antibiotics be considered a special, “protected” regulatory class. This approach would enable unique economic incentives and better antibiotic stewardship requirements to be applied.

b) Surveillance: Better monitoring of resistance rates and antibiotic use in humans and animals is needed to extend the life of current antimicrobials.[i] International and local clinical antibiotic resistance electronic surveillance demonstrations should be funded to test feasibility of providing real-time detection of emerging resistant organisms in hospitals, such as KPC-carbapenemase producing organisms and vancomycin resistant *Staphylococcus aureus*, and enable rapid dissemination of warnings of these threats to other clinical institutions.[ii]

c) Economic incentives for new antibiotic development: Priority antibiotics, diagnostics, and vaccines should qualify for tax relief for R&D, cost reduction and/or support of clinical trials, and extended market exclusivity.

Government funding for applied research on antimicrobial resistance and antibiotic use should be instituted. Particularly strong incentives should be established for antibiotics with a narrow spectrum, novel mechanisms, and those deemed by FDA to have minimal contribution to resistance emergence. R&D at smaller biotechnology companies should also be stimulated.

d) Economic incentives for stewardship: Leadership and increased incentives and funding by Congress and the Administration are long overdue. APUA, IDSA, AMA, and others are currently advocating for legislative action in 2008 through the STAAR Act and PDUFA to provide incentives to new drug development and ensure better stewardship of existing life saving crucial antibiotics. APUA's 2001 FAAIR Report published in CID provides evidence for the need for risk assessment models to consider the full ecology of antimicrobial resistance and use of the precautionary principle in assessing human health risk associated with antimicrobial use in agriculture. Growth promotion in animals should be disallowed.

e) Increased funding for agencies and private organizations working on the problem: It is estimated that over $20 billion is billed to Medicare annually for hospital-acquired infections, many of which are drug resistant. Any government investments to contain resistance will help defray this cost. Funding for public and private groups, especially the CDC, FDA, NIAID, and NIH, and public/private partnerships should be encouraged.

3) Life threatening diseases qualifying for incentives under Orphan Drug Act:

Genes expressing resistance to third-generation cephalosporins, fluoroquinolones and carbapenems have gradually been emerging and spreading. Their convergence in the same strains has begun once again to produce outbreaks of pan-resistant gram-negative bacilli in some parts of the world, and now in the U.S. Occasional clinical bacterial isolates, now mostly Pseudomonas, are resistant to all available effective antibiotics and are thus, virtually untreatable. The difference now is that drug companies are not investing in novel agents. Drugs for gram-negative infections should therefore qualify for incentives under the Orphan Drugs legislation or other favored legislation.[iii]

In conclusion: U.S. national security requires incentives for antibiotic development and stewardship. We need this dual approach applied to antibiotic approvals for both humans and animals to forestall a future of unaffordable drugs and untreatable infections. Antibiotics are unique in that each patient use has an impact on other patients and entire facilities, communities, and the environment. One bold move which could facilitate several unique policy approaches is to separate antibiotics into their own drug category.

The APUA GAARD report published in CID in 2002 stated that large-scale, coordinated, public-private action involving industry, professional societies and public health groups is needed to stop "the shadow of antibiotic drug resistance from lengthening" across our country and the globe. It is seven years later and the U.S. government has yet to respond adequately to protect U.S. patients from galloping resistance. We commend the FDA for its leadership in antibiotic prescription labeling, for calling this hearing, and for supporting the NARMS program. We strongly advocate increases in funding for the FDA to allow more careful consideration of complex antibiotic resistance policy issues.

APPENDIX

[i] Enemies of the United States could collect and propagate antibiotic resistant organisms for use as biological threat agents directly, or more sophisticated foes could use the environmentally derived, resistant organisms as sources of gene transfer into other, potentially more dangerous microbes. Such a threat underscores the need for an international antibiotic resistance surveillance system coordinating the collection and analysis of pathogens as well as environmental and veterinary commensal organisms that may serve as reservoirs for antibiotic resistance in non-pathogenic bacteria. APUA's global Reservoirs of Antibiotic Resistance (ROAR) projects have been established to provide the data needed to better understand the diversity of resistance genes in selected organisms in various targeted geographic regions.

Funded by NIAID and by USAMRIID, the ROAR projects are intended to improve scientific understanding of the role of commensal bacteria in the spread of antimicrobial resistance. This is approached by 1) compiling existing commensal isolate data and literature into a Web-based bioinformatics tool; 2) using statistical methods to analyze the data in order to determine if the frequency of antibiotic resistance genes in commensals can predict the subsequent emergence of antibiotic resistance in pathogenic bacterial populations and 3) encouraging, directing, and funding research efforts to evaluate antibiotic resistance in commensals.

[ii] APUA's Global Antibiotic Resistance Surveillance Program includes the Global Advisory on Antibiotic Resistance Data (GAARD project), Reservoirs of Antibiotic Resistance (ROAR) project, and the State of the State of Massachusetts project.

[iii] Antimicrobial resistance due to ESBL (extended spectrum betalactamase) production is rapidly increasing. According to MYSTIC data, 11% - 30% of strains tested (*Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis*) may be ESBL-producers. ESBLs are mechanisms bacteria use to thwart the treatment of such hospital-associated diseases as pneumonia, septicemia, and intraabdominal sepsis; they are also occurring increasingly in community-associated urinary tract infections. Antimicrobials such as the cephalosporins, which have been historically used to treat these diseases, are losing their power, often leaving only limited treatment options as alternative choices. To ensure effective treatment, laboratories should routinely test for the presence of ESBLs.

Carbapenems are last-line antimicrobial agents. The increase in production by bacteria of metallo-beta-lactamases, which destroy carbapenems, is particularly worrisome. New types of metallo-beta-lactamases are becoming dominant causes of resistance in gram-negative bacilli in Asia, Europe and Latin America. The first metallo enzymes were also detected in the U.S. in late 2002. Metallo-beta-lactamases are usually harbored by species with intrinsic resistances, so that the enzyme genes can carry resistances to other antimicrobial classes, producing various multi-drug-resistant strains for which there are no therapeutic options.

References for Testimony

Alliance for the Prudent Use of Antibiotics. Avorn, JL, Barrett, JF, Davey, PG, McEwen, SA, O'Brien, TF and Levy, SB. Antibiotic resistance: synthesis of recommendations by expert policy groups. Boston, Massachusetts (2001)

Alliance for the Prudent Use of Antibiotics (APUA) Educational Symposium: "Facing the Next Pandemic of Pan-resistant Gram-negative Bacilli" preceding the 42nd Annual Meeting of The Infectious Diseases Society of America (IDSA)
http://www.tufts.edu/med/apua/idsa/report.pdf

Barza, M, Gorbach, S L., (Eds). The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences: A Report of the Facts about Antibiotics in Animals and the Impact on Resistance (FAAIR) Project-The Alliance for the Prudent Use of Antibiotics, *Clin Infect Dis* 34 (Suppl 3):S71-S144 (2002)
http://www.journals.uchicago.edu/toc/cid/34/s3

Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance
Ramanan Laxminarayan and Anup Malani with David Howard and David L. Smith (May 2007).
http://www.extendingthecure.org/downloads/ETC_FULL.pdf

Global Advisory on Antibiotic Resistance Data (GAARD) Report: "Global Antimicrobial Resistance Alerts and Implications" published as a Supplement (2005;41) to Clinical Infectious Diseases
http://www.tufts.edu/med/apua/public_policy/GAARD.pdf

Infectious Disease Society of America. Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates…A Public Health Crisis Brews, Alexandria, Virginia, (2004).

Institute of Medicine. Microbial threats to health: Emergence, detection, and response. Washington, DC, National Academies Press (1998)

Weinstein, RA. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. Emerg Infect Dis 7:188-92 (2001).

See www.apua.org for more information on APUA projects.