

STATEMENT OF THE  
INFECTIOUS DISEASES SOCIETY OF AMERICA  
BEFORE THE FOOD AND DRUG ADMINISTRATION  
PART 15 HEARING PANEL ON  
ANTIMICROBIAL RESISTANCE

APRIL 28, 2008



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The Infectious Diseases Society of America (IDSA) appreciates the opportunity to provide this statement before the U.S. Food and Drug Administration's (FDA) Part 15 panel on the critically important issue of antimicrobial resistance.

IDSA represents more than 8,000 infectious diseases physicians and scientists devoted to patient care, education, research, prevention, and public health. Our members care for patients of all ages with serious and life-threatening infections, including meningitis, pneumonia, tuberculosis, antimicrobial drug-resistant infections, and those with cancer or transplants who have life-threatening infections caused by unusual microorganisms, HIV/AIDS, and other emerging infections.

Antimicrobial resistance is a serious patient safety and burgeoning public health problem. The resistant infections about which Infectious Diseases specialists and other physicians are most concerned at this time are caused by bacteria. For this reason, our statement will primarily focus on antibacterial resistance. IDSA's statement includes a discussion of the antibacterial resistance problem and why Infectious Diseases and other physicians are concerned, the critical need for new products to detect, treat and prevent resistant infections as well as 12 priority recommendations that require FDA's immediate consideration.

**Antibacterial-Resistant Infections: Why IDSA Is Concerned**

Bacterial infections affect hundreds of thousands of Americans and cause tens of thousands of deaths each year, perhaps more. Resistant infections are painful, difficult to treat, and cost many billions of dollars to the U.S. health care system annually. These "bad bugs" have become a silent epidemic in communities and hospitals across the United States as well as around the world. And yet, an astoundingly diminutive amount of federal resources are being committed to address this staggering problem. In fiscal year (FY) 2006, FDA spent only \$24 million on its collective antimicrobial resistance activities, the Centers for Disease Control and Prevention (CDC) spent only \$17.2 million, and the National Institutes of Health (NIH) spent only \$220 million (\$194.5 million of which was spent at the National Institutes of Allergy and Infectious Diseases (NIAID)—4.4% of NIAID's total budget. \$90 million of NIAID's antimicrobial resistance research budget was dedicated to antibacterial resistance research—2.1% of NIAID's total budget).

The bacteria of greatest concern include multi-drug-resistant *Staphylococcus aureus* (MRSA), resistant *Escherichia coli* (*E. coli*), *Acinetobacter baumannii* (which is

threatening soldiers returning from Iraq and Afghanistan), resistant *Klebsiella species* (which appear to have originated in or near Brooklyn and now are spreading across the East Coast and into the Midwest), extensively drug-resistant tuberculosis (XDR-TB), *Clostridium difficile*, *Enterococcus faecium*, *Enterobacter species*, and resistant *Pseudomonas aeruginosa*. There are many others.

Although primarily affecting ill people in hospitals, a growing number of the victims of drug-resistant bacteria, such as MRSA, are people in the community and outside hospitals, including healthy athletes and children. A recent study in the Journal of the American Medical Association (October 17, 2007) demonstrates that more than 94,000 people are infected and nearly 19,000 die annually from MRSA alone around the country – more deaths than those caused by emphysema, HIV/AIDS, Parkinson’s disease and homicide. New national surveillance data from the CDC demonstrate that an incredible 80% of *E. faecium* associated with device-related healthcare-associated infections (HAIs) were resistant to vancomycin. More broadly, these new data demonstrate high rates of antimicrobial resistance in the gram-negative pathogens associated with device-related HAIs. Disturbingly, analysis of national data indicated that twenty-six to thirty-seven percent of *A. baumannii* were carbapenem-resistant, as was ten percent of *K. pneumoniae*. Thirty percent of *P. aeruginosa* were resistant to fluoroquinolones.

### **Antibacterial Drug Portfolio: Why IDSA Is Concerned**

Of serious concern, Infectious Diseases physicians are alarmed by the prospect that effective antibacterial drugs may not be available to treat seriously ill patients in the near future. Since their discovery, antibacterial drugs have dramatically reduced the morbidity and mortality associated with bacterial diseases, saving millions of lives and easing patients’ suffering. However, over time, certain classes of drugs are losing their effectiveness to increasingly resistant infections. Until recently, the pharmaceutical industry’s research and development (R&D) efforts counteracted this phenomenon by developing new drugs in time to treat bacteria that became resistant to older antibacterial drugs. However, that is no longer the case. Unfortunately, both the public and private sectors appear to have been lulled into a false sense of security based on past successes.

The potential crisis at hand is the result of a marked decrease in industry R&D, government inaction, and the increasing prevalence of resistant bacteria. It takes 8 years to develop a new antibacterial drug. Thus, today we should be planning for our pharmaceutical needs of 2012-2015. Given the state of the current pipeline, our future looks bleak. To call attention to the resistance problem and the diminishing pipeline, in 2004, IDSA launched its “Bad Bugs, No Drugs” advocacy campaign by issuing a landmark report and several subsequent articles to highlight the brewing patient safety and public health crisis. ([www.idsociety.org/badbugsnodrugs](http://www.idsociety.org/badbugsnodrugs)).

FDA has acknowledged there is problem in the antibacterial drug pipeline. In the agency’s March 2004 Critical Path report “Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products”, the agency reported that “product development in areas crucial to public health goals, such as antibiotics, has

slowed significantly during the past decade.” However, since 2004, the agency has dedicated insufficient time and resources to solve the resistance or pipeline problems. In fact, if anything, the Agency’s recent actions have produced greater cause for worry as growing uncertainty about FDA’s anti-infective drug review process mounts.

It is frustrating to see patients with life-threatening infections and the toll it takes on their lives and on their families and friends, or to see children and adults die when we have the resources and the tools to reduce the impact of these diseases. We cannot stop the development of antibacterial resistance – bacteria will continue to mutate in response to antibacterial drug use. However, we can slow the pace of the rise in antibacterial resistance, if we have the will to act.

### **The Path Forward**

Antibacterial resistance and the diminishing antibacterial pipeline are complex and multi-dimensional problems. Multi-pronged solutions are required to sufficiently limit the impact of antibacterial resistance on patients and the public and to spur the development of products to address antibacterial resistant infections. Such efforts include:

- removing disincentives in the antibacterial drug review process by reestablishing consistency, predictability and timeliness;
- providing economic and other incentives to spur the development of new products in this area (e.g., antibacterial drugs, relevant diagnostic tests, and vaccines);
- significantly strengthening federal research in new, relevant rapid diagnostics as a means to reduce the number of patients needed for antibacterial drug clinical trials;
- creating an antimicrobial resistance strategic research plan that establishes priorities and significantly strengthens collaborations between FDA, NIH, CDC, the Departments of Agriculture, Veteran Affairs, Defense and the Environmental Protection Administration.
- educating physicians, patients, and parents about the appropriate use of antibacterial drugs;
- developing and applying infection control and immunization policies and practices to prevent transmission;
- improving our collection of data regarding clinical, veterinary and human antibacterial use, and other data;
- protecting antibiotics of importance to human health from being used in agriculture;
- improving surveillance efforts to detect and monitor the emergence of resistance; and
- developing safer alternatives to antibacterial drug uses in agriculture.

Implementing many of these solutions will require significant attention, resources, and, in some cases, substantial political will to overcome special interests in favor of public health and patient safety.

In 2001, the Administration recognized the gravity of the problem and developed a federal “Action Plan to Combat Antimicrobial Resistance,” an effort led by CDC, FDA, and NIH. Unfortunately, very limited progress has been made toward implementing the Action Plan’s 13 Top Priority Action Items, let alone the remainder of the 84 action items. Moreover, in 2000, FDA’s own Task Force on Antimicrobial Resistance issued a report (<http://www.fda.gov/oc/antimicrobial/taskforce2000.html>) containing nine (9) recommendations which, if implemented, could have helped significantly to address the antimicrobial resistance problem. Unfortunately, the Agency has made little progress toward implementing these recommendations since 2000.

Below are twelve additional recommendations that IDSA believes will go far toward addressing the antimicrobial resistance and pipeline problems. Within these recommendations are several critical steps that FDA can take immediately.

The United States Government, including FDA, can no longer take a business-as-usual approach toward addressing the antimicrobial resistance problem. Following today’s Part 15 hearing, it is imperative that the agency dedicate sufficient resources to implement the Action Plan’s recommendations, FDA’s own recommendations from 2000 as well as the additional recommendations that IDSA outlines below.

### **IDSA’s Twelve Recommendations For FDA’s Immediate Consideration**

[The following recommendations are not listed by priority ranking. They are listed chronologically as they will be presented by IDSA’s presenters.]

#### **Recommendation # 1 *FDA Should Work Aggressively To Re-Establish Consistency, Predictability, and Timeliness In The Antibacterial Drug Review Process.***

Significant uncertainty exists within the agency’s antibacterial human drug review process, which we fear is shaking the foundation of the nation’s antibacterial pharmaceutical industry. The agency must move quickly to reestablish consistency, predictability, and timeliness to this process which IDSA believes requires the attention and leadership of the director of the Center for Drug Evaluation and Review as well as an infusion of additional staff and resources. IDSA has heard from many pharmaceutical industry representatives that FDA has lost credibility by throwing out existing policies without having new policies available to replace the old, rejecting prior agreements with companies, and employing endless delays including in the issuance of clinical trial guidances. Time delays are costing millions and threatening bankruptcy for some companies. FDA must move rapidly to restore trust by making public its plan to resolve internal disincentives to antibacterial drug discovery and development. The plan should include the agency’s priorities for action.

#### **Recommendation # 2 *FDA Should Strengthen Critical Path And Other Research, Establish Research Priorities With NIH, CDC, USDA, and Other Agencies And Collaborate More Often With These Agencies On Antibacterial Resistance and Drug Pipeline-Supportive Research.***

In 2000, FDA's Task Force on Antimicrobial Resistance reported "In hearing about the efforts of multiple centers, it also became clear that coordination of antimicrobial resistance research, both within FDA and with sister government agencies and academia, is currently largely informal." In IDSA's estimation, little has changed to formalize the U.S. antimicrobial resistance research agenda and to establish and publicize U.S. priorities. For this reason, in June 2007 IDSA proposed the creation of an antimicrobial resistance strategic research plan to strengthen existing epidemiological, interventional, clinical, translational and basic research efforts in a letter to Drs. Anthony Fauci, NIAID Director, and Julie Gerberding, CDC Director, (<http://www.idsociety.org/WorkArea/showcontent.aspx?id=4642>). FDA has a critical role to play in that effort, and we urge FDA, NIH, CDC, the U.S. Department of Agriculture (USDA), and other relevant agencies to move immediately to establish a Blue Ribbon Panel to establish U.S. research priorities and create a strategic research plan.

Even without such a strategic plan, FDA should act now to support research that can help lead to a reduction in the number of patients necessary for antibacterial clinical trials. Such research should include validation of endpoints such as quality of life, length of stay, duration of fever, time to elimination of pathogen, patient-reported outcomes, etc. as well as the development of new, rapid diagnostics. The agency should seek and strengthen collaborations with NIH, CDC, USDA and other agencies on studies that will address resistance and support the antibacterial drug pipeline. Finally, FDA should publish a summary of the antimicrobial resistance/pipeline research efforts it currently has underway under its Critical Path and other initiatives.

**Recommendation # 3 *FDA Should Take Immediate Action To Update Antibacterial Clinical Susceptibility Concentrations.***

Physicians need accurate information on antibacterial clinical susceptibility concentrations ("breakpoints") to use antibacterial drugs wisely. Patients' safety and lives are on the line. Given a new requirement included in the FDA Amendments Act, it is incumbent upon the agency to establish workable processes for expeditiously updating antibacterial breakpoints as well as to publish its methodology for setting breakpoints. FDA staff's recent inventory of antibacterial labels has uncovered that out of the more than 100 currently approved antibacterial labels more than 70 contain breakpoints that are out-of-date.

Prior to 2006, FDA's Center for Devices and Radiological Health (CDRH) allowed susceptibility test device manufacturers to include both FDA-established breakpoints listed in package inserts at the time of the drug's approval as well as the more up-to-date breakpoint recommended by the Clinical Laboratory Standards Institute (CLSI) (formerly NCCLS). CLSI, a 501(c)(3) non profit organization, is a recognized standard setting body comprised of experts in infectious diseases and clinical microbiology. CLSI is not affiliated with IDSA. In 2006, FDA began to require that CLSI submit citizen petitions to the agency when recommending updated breakpoints. In IDSA's estimation, the new

process has been a failure as FDA has taken limited definitive action on the five CLSI petitions submitted to date.

The agency should explore several options available to it for updating breakpoints including:

- establishing a less-cumbersome process for reviewing and accepting CLSI's recommendations;
- creating FDA's own scientific board of external experts comprised of infectious diseases clinicians, microbiologists, pharmacologists, and others who understand the clinical impact of changes in the interpretations of the MIC. The board could help the agency update breakpoints and/or review and approve breakpoints recommended by CLSI or other appropriate entities;
- contracting out some of the activities needed to update breakpoints through organizations such as CLSI. Infusing some of the agency's patient safety funding into CLSI's effort could help to more quickly address out-of-date breakpoints.

Specifically, IDSA urges FDA to:

- review and update antibacterial drug breakpoints on a regular basis as clinical need dictates, but no less frequently than every 5 years
- return to purchasing from private vendors the critically needed susceptibility data used to update breakpoints;
- require pharmaceutical sponsors (both pioneer and generic) to provide any such additional data as may be needed to update breakpoints quickly; and
- immediately publish its methodology for setting breakpoints, which previously has not been made public. IDSA members have heard statements from FDA officials that such methods are "not written down anywhere". This is unacceptable and only helps to demonstrate the lack of attention and sufficient resources the agency has devoted to this critical patient safety responsibility over the last several decades.

**Recommendation # 4 *FDA, Working With Other Agencies Represented On The Interagency Task Force On Antimicrobial Resistance, Should Establish A Public Health Antimicrobial Advisory Board Of Outside Experts To Advise The Task Force In Its Efforts.***

Antimicrobial resistance is a complex, multi-dimensional problem. Addressing the problem will require expertise from the infectious diseases, medical (including hospital and community-based physicians), veterinary, public health, research, pharmaco-economic, and international health communities. The private sector provides incredible expertise in each of these fields which would be extremely valuable to the Interagency Task Force on Antimicrobial Resistance in setting and maintaining priorities and in carryout out its responsibilities. For this reason, IDSA strongly recommends that FDA, NIH and CDC create an advisory board to advise the existing Interagency Task Force on Antimicrobial Resistance. Such an advisory board should meet with Task Force

members on a regular (biannual) basis. For a list of the advisory board's potential duties and responsibilities see H.R. 3697/S. 2313, the "Strategies to Address Antimicrobial Resistance Act".

**Recommendation # 5 *FDA Should Reevaluate And Strengthen Regulatory Requirements On Data Collection Of Antibacterial Use In Humans.***

FDA should reevaluate (including by holding a public workshop) the manner by which it collects antibacterial drug human use data from pharmaceutical companies to determine if it may be collected in a manner and format that is reliable and comparable and which best ensures it is of maximum value to the study of antibacterial resistance development (e.g., using defined daily doses, collected by calendar year). In addition, the agency should seek an agreement with IMS Health or another private vendor to obtain antibacterial drug human use data in a manner whereby such data may be shared with the Interagency Task Force on Antimicrobial Resistance as well as with members of the advisory board proposed in Recommendation #4. Of course, members of the Task Force and advisory board will need to sign confidentiality agreements.

**Recommendation # 6 *FDA's Center For Veterinary Medicine Should Move Quickly To Issue Its Long-Delayed Draft Regulation And Guidance #146 On Collection Of Data On Antibacterial Use In Animals.***

FDA's Center for Veterinary Medicine (CVM) should move forward immediately to issue for public comment its draft Guidance #146 and draft regulation developed in 2001 and 2002, which were intended to redefine the type of antibacterial distribution data that animal drug manufacturers must provide to the agency on antibacterial drug use in animals. The draft regulation and guidance have been held up within the agency since 2002 for unknown reasons. It is extremely important that animal antibacterial drug use data be collected in a manner and format that is reliable and comparable and which best ensures it is of maximum value to the study of antibacterial resistance development (e.g., collection using "defined daily doses," by species and indication, and based on a calendar year model as opposed to the anniversary date of the product's approval). The collection of such use data will make information currently collected under the National Antimicrobial Resistance Monitoring System of greater relevance as it can be used to show where there may be correlations between antibacterial use and the development of resistance. This likely will be one of those instances where the Administration will need to muster substantial political will to overcome special interests in favor of public health and patient safety.

**Recommendation # 7 *FDA/CVM Should Update Guidance #152 To Include Missing Criteria Concerning The Relative Importance Of Antibacterials In Human Medicine.***

FDA's CVM should hold a public workshop to bring together experts in infectious diseases human and veterinary medicine as well as other key stakeholders to reassess the criteria currently contained in CVM's Guidance #152 with regard to their potential

impact on resistance patterns in human drugs. Guidance #152 is the framework document used for the approval of antibacterial drugs for use in animals. In particular, the agency should reconsider the criteria used to categorize antibacterial drugs as “critically important” and “highly important” to human health and whether the scope of such criteria should be broadened beyond enteric pathogens. Additionally, the agency immediately should change the classification of cefepime to “critically important” to be consistent with the World Health Organization’s classification of this drug. Cefepime is the only 4<sup>th</sup> generation cephalosporin in use in the United States in humans, and IDSA and other expert organizations have emphasized the threat posed both to cefepime and to 3<sup>rd</sup> generation cephalosporins by the prospect of 4<sup>th</sup> generation cephalosporin use in livestock.

**Recommendation # 8 *FDA Should Move Forward Immediately To Implement Its Own Recommendations On Antimicrobial Resistance.***

In December 2000, FDA’s Task Force on Antimicrobial Resistance issued a report (<http://www.fda.gov/oc/antimicrobial/taskforce2000.html>) containing priority recommendations the agency was to implement to address the antimicrobial resistance and pipeline problems. Few of these recommendations have been implemented to date. Such inaction can only be interpreted as demonstrating the Agency’s past lack of commitment to a brewing crisis that Infectious Diseases physicians believe should be a significant priority of the U.S. Government. IDSA hopes that along with the Agency’s desire to hold today’s Part 15 hearing, we are witnessing a turning point in the Agency’s thinking and a demonstration of its desire to tackle these critical patient safety and public health problems. To confirm this, the Agency should act immediately to dedicate the necessary resources necessary to implement its own Task Force’s recommendations as well as the additional recommendations that IDSA is proposing today.

**Recommendation # 9 *FDA Should Require That Antibacterial Impact Statements And Management Plans Intended To Predict And Limit Resistance Development Be Included In Human Drug Applications.***

FDA should require antibacterial drug sponsors (both pioneer and generic) to submit as part of their drug applications a resistance impact statement that attempts to predict how approval and use of such antibacterial drug may impact upon the development of resistance. Pioneer and generic sponsors of human drugs also should be required to submit antibacterial use management plans intended to be used to limit the development of resistance associated with the drug’s use. Such impact statements and management plans should be made public so that researchers may use each to study and strengthen our understanding of the science of predicting resistance development as well as how to prevent and control its development. Neither the impact statement nor management plan should be used for enforcement purposes.

**Recommendation #10 *FDA Should Commission A Study Through The Tufts Center On The Study Of Drug Development (Or Another Appropriate Entity) To Obtain Expert Recommendations As To Which Incentives Are Necessary To Strengthen The Antibacterial Drug, And Relevant Diagnostics And Vaccine Pipelines.***

New products (antibacterial drugs, vaccines, diagnostic tests) are critically needed to treat and prevent serious and life-threatening antibacterial resistant infections as well as to rapidly detect the organism causing that infection. New rapid diagnostic tests will be particularly useful in helping to reduce the numbers of patients needed to demonstrate the safety and effectiveness of antibacterial drugs in clinical trials.

Tax credits for R&D, extensions on periods of market exclusivity, strengthening of intellectual property rights, priority FDA review vouchers, grants, prizes and other incentives have all been offered as potential incentives. IDSA does not have all of the answers as to which combination of incentives will ultimately be successful.

Within the federal Interagency Task Force's Action Plan to Combat Antimicrobial Resistance issued to 2001, FDA was designated to take the lead on implementing two of the thirteen "Top Priority Action Items." These include:

***"Top Priority Action Item*** — *Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs in human and animal medicine for new AR products (e.g., innovative drugs, targeted spectrum antibiotics, point-of-care diagnostics, vaccines and other biologics, anti-infective medical devices, and disinfectants)."*

***"Top Priority Action Item*** — *Identify ways (e.g., financial and/or other incentives or investments) to promote the development and/or appropriate use of priority AR products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate."*

To date, FDA has done nothing to address either Top Priority Action Item.

Arguably, neither FDA nor any federal agency is well-placed to examine and make recommendations about the type of incentives that will promote antibacterial drug development. However, the Tufts Center for the Study of Drug Development commonly studies pharmaceutical pipelines and the pharmacoeconomic and non-economic factors that spur drug development. For this reason, IDSA strongly urges FDA to commission a study through the Tufts Center (or some other similar entity, if one exists) seeking a report on strengths and weaknesses in the antibacterial and related diagnostics and vaccine R&D pipelines with a particular emphasis on products needed to treat, detect, and prevent serious and life-threatening infections. The study also should provide recommendations as to what combination of incentives, considering each phase of product development, will work to spur greater R&D of such products among the biotechnology, pharmaceutical, vaccine, and diagnostics industries as well as within academic settings.

**Recommendation #11 *FDA Should Immediately Clarify Its Policies Under The Orphan Drug Act Relating To Serious and Life-Threatening Infectious Diseases Associated With Antibacterial Resistant Organism.***

FDA should immediately clarify how it calculates prevalence of cases under the Orphan Drug Act related to serious and life-threatening infectious diseases associated with antibacterial resistant organisms. Agency officials have provided contradictory messages on this point, which has had a negative impact on IDSA's ability to advocate for the adoption of new statutory incentives to spur R&D on products that will protect patient safety and public health.

**Recommendation #12 *FDA Should Effectively Communicate Its Professional Judgment As To The Funding It Needs To Sufficiently Address The Antimicrobial Resistance Problem.***

The Department of Health and Human Services (HHS), including FDA, NIH, and CDC need to effectively communicate the resources the department and agencies need to address antimicrobial resistance. Last year, two members of Congress [Reps. Jim Matheson (D-UT) and James McGovern (D-MA)] asked Secretary Leavitt during an HHS' budget hearing for FDA's, NIH's, and CDC's professional judgments concerning the amount of funding each agency needs to implement their respective responsibilities under the federal Action Plan to Combat Antimicrobial Resistance. It is unclear whether FDA ever submitted its professional judgment request to HHS. However, it is clear that HHS did not submit any professional judgments to the Congressmen.